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DRUGS and DRUG ABUSE

COX
JACOBS
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MARSHMAN

A Reference Text

ADDICTION RESEARCH FOUNDATION

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A Reference Text

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TERRENCE C. COX
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ADDICTION RESEARCH FOUNDATION
TORONTO

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Foreword

In accepting the invitation to write the foreword to *Drugs and Drug Abuse*, I did so, not with the confidence of someone who is authoritative in the field, but with the feeling of gratitude that at last there was a professionally written compendium available upon which I could rely for the information I require in the exercise of my judicial duties and also to satisfy my natural curiosity about drugs. This volume will serve both of my purposes admirably.

Drug offences have constituted a major ingredient of the last 16 years of my professional life, as a prosecutor, a defence lawyer, and now a judge. Until the publication of this handbook, I, like others involved in the administration of justice, have had either to master the technical pharmacological literature of drugs and their abuse, or rely on commercially popular publications, which are more often a treatise for the pro or con bias of their author than a reference book of facts. In spite of effort, I have never mastered the technical literature, nor have I ever trusted popular publications. With this finely researched book, I can find dependable, easily read, and well cross-referenced material about virtually any drug I am likely to deal with in law.

While the impetus for the book may have been a request by judges, it has been written so as to be of great value to lawyers and police officers, as well as to a much larger audience of social workers, counselors, and teachers who require source information in order to deal with the wholly uninformed. As well, the handbook will, I hope, dispel some of the more popular street myths about individual drugs. The easily readable language should de-mystify a subject which ought to be widely understood by the whole justice community and that larger audience I mention.

I tender the thanks of the members of our court for the years of effort and scholarly discipline which the four authors have devoted to this volume and to add that our request has been answered more amply than ever anticipated. I feel confident in tendering the appreciation of the legal profession, the law enforcement agencies, social work and counseling disciplines, and the teaching community, even before they have had access to this worthy work.

His Honour Arthur C. Whealy
County and District Court Judge
Province of Ontario

Preface

The County Court Judges of York, Province of Ontario, approached the Addiction Research Foundation some time ago with the request that the Foundation create a reference book that would be of use to those on the bench who had to deal with alcohol and drug-related cases. This "handbook" was not meant to deal with legal matters but rather was designed to provide judges, lawyers, and other concerned professionals, such as physicians and social workers, with a guide to the many issues and pertinent facts associated with psychoactive drug use and abuse.

Pharmacology is the main focus of the book; however, psychology, medicine, chemistry, epidemiology, and a number of other disciplines have all made significant contributions to the total picture we present. Understanding drug abuse is a complex task, and the relatively new field of addictions research is not encompassed by any one science.

The introductory chapter (section 1), "Understanding Drug Use," is a general outline and exploration of the basic issues involved in drug use, drug abuse, and drug dependence. A close study of this chapter will help the reader to understand more deeply the remainder of the text.

Following the overview chapter on drug use are chapters on the various classes of psychoactive drugs (section 2): central nervous system depressants (i.e., sedative/hypnotics and the minor tranquillizers), hallucinogens, mood modifiers (i.e., antidepressants and the major tranquillizers), narcotic analgesics, and stimulants. Each of these chapters provides extensive information about one specific class. We recommend that these chapters be read prior to the individual drug articles (sections 3, 4, and 5), for this general background knowledge will enhance the reader's understanding of the issues associated with the individual drugs.

The psychoactive drugs selected for inclusion in section 3 of the book are those that have the greatest currency/popularity in North American society today. Of necessity, this list will change over time to reflect fashion, drug use legislation, and new discoveries by the pharmaceutical industry, and at some point in the future it will be necessary to revise the book to reflect new scientific data as well as new patterns of use. It is very likely, however, that the major drugs that are described in this section will continue to dominate the drug use/abuse patterns of our society for many years to come.

We have tried to lay a basis of understanding as to the nature of these drugs and the effects they have on the individual and to some extent on society as a whole. As well, we have employed the concept of "abuse potential" to circumscribe the various factors that contribute to the popularity of any given drug and to the incidence of its use and abuse.

A few drugs are included in section 3 for special reasons other than prevalence of use. It may be argued that the nonbeverage alcohols (isopropyl alcohol and methyl alcohol) are of limited interest, since they are only infrequently abused; they are nevertheless notable for their highly toxic properties. Two other drugs described in section 3—naloxone and disulfiram—have no discernible psychoactive effects that would encourage abuse. However, naloxone is included because it is important in the management of opiate abuse, and disulfiram because it is now so often used in the treatment of alcoholism.

The drugs described in the briefer articles in section 4 are generally of less importance in the overall context of abuse than those in section 3. Some, such as hydrocodone (a narcotic analgesic found in some cough syrups), which until recently had not been widely abused, may be gaining in popularity. Others, such as phenmetrazine (a moderately potent stimulant), now seem to be fading in popularity. Still others, such as methyprylon (a sedative/hypnotic), are somewhat less frequently abused than related drugs with similar properties. Opium is primarily of interest because it yields the major opiates—morphine, codeine, and heroin.

Most of the drugs found in section 5, "Additional Drug Notes," attract limited attention in our society, but may come to the attention of health and legal professionals from time to time.

Section 6 contains an Appendix, which offers a comprehensive listing of the Canadian and American trade names for most of the legitimately marketed psychoactive drugs discussed in this book, as well as a Medical/Scientific Glossary and a Glossary of Street Drug Language. We hope that the Medical/Scientific Glossary will be of help to those readers who have only a layman's familiarity with medical and chemical terminology. As a rule, however, we have endeavored to explain as many terms as possible as they occur within the text.

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Section 1

Understanding Drug Use

Understanding Drug Use

A variety of chemical, pharmacological, and behavioral factors influence the nature and outcome of psychoactive drug use. The impact of drug dependence and drug toxicity on the individual user, on specific drug-using populations, and on society can be adequately understood only if we examine the many dimensions of the drug-use situation: the actual drug involved, its pharmacological effects, the hazards of particular patterns of use, and the characteristics and risks of the method of administration. Moreover, since many situations involve more than one drug, it is important to consider the interactions among drugs both within the same drug class and across different classes, for some of these interactions are potentially dangerous.

Our knowledge of these fundamental issues has developed through research in that branch of science known as pharmacology. The application of knowledge derived from this study permits an effective response by a broad spectrum of medical and nonmedical professionals, paraprofessionals, and others in practical situations involving drug users. Basic pharmacology explores the nature and effects of the drug substances as they impact on the human physiological system. However, perhaps the most fundamental and persistent question which basic pharmacology must address and to which the answer is continually evolving is “What is a drug?”

DEFINITION OF THE CONCEPT “DRUG”

The ancient Greeks called drugs *pharmakon*, a word which meant both poison and medicine. Similarly, *pharmakeuein* was either the practice of witchcraft or the use of medicine depending on the context. These simplistic concepts, reflective of a certain ambivalence, represented the attempt of Greek society to come to terms with the powerful effect of drugs on the mind and body of the individual.

Even in more recent times, society has had great difficulty in arriving at one satisfactory definition of the word “drug.” For many people, a drug is simply whatever the doctor prescribes to treat their disease or discomfort. Such a definition, however inoffensive, does nothing to alleviate the confusion that arises whenever a precise answer to this question becomes important to us.

The question “What is a drug?” is complicated by the fact that various substances not usually considered as drugs may function as drugs under certain circumstances—for example, foods and beverages, or solvents and aerosols. For instance, most people think of alcohol merely as a beverage which with normal use could easily be interchangeable with other beverages. Yet many people often prefer alcohol over other beverages because it gives rise to a feeling of relaxation and helps to remove inhibitions in close social interactions, effects resulting from its activity as a central nervous system (CNS) depressant. When people drink it for these reasons, it becomes reasonable to view it as a drug. Less commonly, alcohol can be termed a drug when it is prescribed for its high energy content in the intravenous feeding of patients with special medical problems. Other food substances such as glucose, salt, and vitamins can be termed drugs when they are used respectively in the treatments of diabetes, shock, and malnutrition. Regular, heavy use of caffeine-containing beverages and of tobacco supports the view that these substances are commonly used as drugs to produce certain psychological effects related to central nervous system stimulation.

The gases in aerosol cans and the solvents found in household and industrial cleaners (e.g., petroleum distillates, acetone, and trichloroethane) can be reasonably considered as drugs when they are inhaled, whether accidentally or deliberately. If they are carelessly handled, spilled in an enclosed space, or taken intentionally for their mood-altering effects, in sufficiently large quantities they affect the functioning of the brain in much the same way as the sedative/hypnotic and anesthetic drugs.

On the basis of the above examples, it is evident that the human intent behind use may serve as a criterion in determining whether and under what circumstances substances should be called drugs. It follows from this viewpoint that, in the case of both pharmaceutical preparations and naturally occurring substances, a substance is a drug whenever its use is intended primarily to bring about change in some existing process or state, be it psychological, physiological, or biochemical. The intended modification can be directed toward changes in medical, behavioral, or perceptual states and for either therapeutic or nonmedical purposes. In the case of foods, beverages, and industrial chemicals, a substance can be considered a drug when its use is diverted toward bringing about these types of changes.

It is evident from these definitions that a vast number of substances from a wide variety of sources may be considered to be drugs. However, throughout all of the discussions which follow in this book, we shall, with a few exceptions, consider only those drugs which have, either as primary or secondary characteristics, mood-altering properties.

SOURCES OF PSYCHOACTIVE DRUGS

Psychoactive drugs can be divided into three major types, according to source: naturally occurring, semisynthetic, and synthetic.

1. Certain plants and animal tissues contain psychoactive drugs; in some cases the crude material is used as the drug preparation, while in other cases the drug substances are extracted and purified. These drugs are described below as *naturally occurring.*
2. Chemical manipulations of psychoactive substances which have been extracted from natural materials may result in drugs with somewhat different properties. These drugs are called *semisynthetics.*
3. Psychoactive agents neither found in nature nor derived from natural psychoactive agents are known as *synthetics*; they are created entirely by laboratory manipulation of two or more relatively simple chemicals which in themselves are usually psychoactively inert.

Naturally Occurring Psychoactive Substances

Plants are important sources of mood-modifying drugs. Both primitive and modern societies have relied heavily on plant resources for both medical and nonmedical drugs. In China, for example, the CNS stimulant ephedrine has been extracted from a local plant, *ma huang* (*Ephedra equisetina*), and used in traditional medicine for thousands of years. Ephedrine has also been widely used in Western medicine since its introduction at the turn of the century; the ephedrine used initially was isolated from plant material, but that used nowadays is synthesized in a chemical laboratory. The stimulant cocaine, contained in the leaves of the *Erythroxylon coca* shrub, has been in both medical and nonmedical use in Peru for hundreds of years. It is both a local anesthetic and a stimulant. The active alkaloid, cocaine, is easily extracted from the plant by chewing or pressing the leaves. Opium and its chief alkaloid, morphine, have long been in use as analgesics and euphoriants in medical and nonmedical circles. It is a relatively simple matter to extract these drugs from the resin in the unripe seed pods of the opium poppy, *Papaver somniferum.*

Most of the natural psychoactive drugs have been in use for centuries. It is worth noting that folk medicine discovered and took advantage of the drug effects without knowledge of their chemical nature and without the advantages of the sophisticated analytical techniques and international searches now utilized in pharmaceutical and pharmacological investigations.

Semisynthetic Psychoactive Drugs

Chemists often use a substance derived from a natural source as a starting material for the chemical synthesis of some other drug substance. Heroin (diacetylmorphine), for example, is prepared in the laboratory from the natural product, morphine, in chemical combination with another substance, acetic anhydride or acetyl chloride. Similarly, LSD (lysergic acid diethylamide) is derived from certain ergot alkaloids — naturally occurring substances in certain *Claviceps* fungi which grow on grains. The naturally occurring ergot alkaloids are used to control postpartum hemorrhage and restore normal uterine tone and to treat migraine headaches. LSD is an example of a semisynthetic derivative with pharmacological actions which transcend those of the substances from which it is derived.

Synthetic Psychoactive Drugs

Synthetic drugs are prepared entirely from relatively simple chemical substances in a laboratory; they do not depend on plant or animal substances as a starting material. Many of the drugs prepared in this way do not occur in any natural state and have been designed in such a way as to have some particular pharmacological property or combination of properties which cannot be obtained in naturally occurring drugs.[1] Methadone is a synthetic compound which was developed initially in Germany during World War II, when the opium poppy resin needed to produce morphine was difficult to obtain. Dextromethorphan is an example of an entirely synthetic cough suppressant; while structurally related to the opium alkaloids, it is designed to combat cough effectively without the risk of dependence—a disadvantage of most cough suppressants derived from opium.

Within any pharmacological drug class, there may be examples of drugs obtained from each of these three types of source. For example, opium and morphine are naturally occurring analgesic psychoactive drugs. Heroin, derived from morphine through chemical modification, is a semisynthetic drug with similar properties. Methadone and meperidine, again with similar properties, are totally synthetic. Although these substances are not identical, they can be used interchangeably for the relief of certain types of pain and are all sought by abusers principally for their euphoriant effects.

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[1] Some drugs which exist in nature may also be produced synthetically, if the synthetic method is more economical or more practical.

LEGAL (ETHICAL) AND ILLEGAL MANUFACTURE OF PSYCHOACTIVE DRUGS

The term "pharmaceutical industry" is commonly used to designate the group of legally sanctioned industrial/commercial enterprises which prepare and market drugs. Some companies carry out only the processes which result in preparation of large amounts of active drug substances; these they sell in bulk to other companies which prepare individual dosage units (tablets, capsules, vials of solution, syrups, suppositories, etc.). The company which prepares the dosage units may itself market them to hospitals, pharmacies, and medical, dental, and veterinary practitioners, or it may wholesale them to other companies involved in distribution. Many large pharmaceutical companies carry out all manufacturing functions as well as marketing and distribution.

Similar kinds of functions are carried out in the illicit drug industry. Some individuals or groups specialize in large-scale production of the drug substances, leaving others to prepare the dosage forms.

In Canada, the legal and ethical manufacture of drugs takes place in laboratories or factories which must comply with government standards. The drugs are formulated into stable preparations of known strength and purity so that dosages can be prescribed with accuracy and confidence and can be relied on by the user. In addition, the products are carefully labeled with instructions for storage and appropriate use, in many cases with an expiry date. Most are intended for use by those following a medically supervised program. Many may be obtained only with a prescription. Over-the-counter drugs, prepared under the same strict control, are intended for safe self-medication of minor ailments.

Illegal manufacture of psychoactive drugs takes place in clandestine laboratories where very often little attention may be given to matters of purity, safety, or reliability. In some cases the production methods used are crude and outdated and the skills of the producer quite limited. Indeed, anyone with a rudimentary knowledge of chemistry can manufacture drugs, provided the clients' standards of acceptability are not very high. However, it must be acknowledged that in certain large and well-organized illicit enterprises, both the equipment and the chemical skills are very sophisticated. But overall, with the products of illicit laboratories, buyers are uncertain what drug they are getting, in what strength, or with what it has been adulterated.

Illegal manufacture is directed ultimately toward the dealers ("pushers") who sell the drugs on the street. However, a secondary market for some drugs comprises a very small number of dishonest pharmacists or wholesalers who buy counterfeit drugs that are considerably cheaper than the regular pharmaceuticals and pass them off to customers as the legitimate product.

It is important to note that not all drugs available on the street are manufactured illicitly. Many legitimate pharmaceutical products are diverted to the illicit market in the course of distribution, stolen, or obtained on forged prescriptions.

IDENTIFICATION AND ANALYSIS OF DRUGS

Visual Identification of Drug Preparations

Generally speaking, legally produced drugs can be identified much more easily than illegal drugs, for illegal drugs are usually unlabeled and devoid of the identifying marks which are being used increasingly for the legal products. Occasionally, however, illicit producers do attempt to identify their products for the street market: for example, "Raggedy Ann" was a dosage form of LSD on blotting paper bearing the drawing of a doll. Illicit producers may also counterfeit the size, color, shape, and markings of the dosage form for a particular legal product, using discarded punch-and-die sets or using the original capsules emptied and refilled or adulterated. In most cases, it is impossible to identify visually a drug substance that is encountered outside of legitimate channels.

The Problem of Reliability in Illegal Drugs

On the illegal drug market, reliability is a serious problem for the buyer, because neither buyer nor pusher can be certain of the identity, purity, or potency of the drug being sold.

Street-drug analysis facilities in both Canada and the United States report regularly that a substantial proportion of samples submitted to them for analysis do not contain the drug they were represented to be. Drugs submitted to Canadian laboratories as mescaline are almost always LSD, PCP (phencyclidine), or a combination of the two. LSD and certain amphetamine-like substances have been substituted for MDA (methylenedioxyamphetamine), another hallucinogen. A few years ago in Canada, a number of hallucinogen users died when they took PMA (paramethoxyamphetamine), a highly toxic amphetamine analogue, possibly in the belief that they were taking MDA.

Purity is most likely to be a serious problem when the drug is in liquid form intended for injection. Unsanitary material and insoluble diluents are a major source of drug-related infections and associated tissue damage among those who inject drugs. Even with drugs taken orally, however, it is possible to become extremely ill from impurities mixed in with the desired drug.

In addition, even when the desired drug is sold to the user with no misrepresentation and without impurities, there remains the question of potency or dose level. The ideal drug preparation from the user's viewpoint is one potent enough to give the desired effect but not so potent that it constitutes an overdose. If the dose is at the appropriate level, little damage is likely to be sustained. With drugs which create physical dependence, such as heroin, if the potency of the dose is far below the accustomed level, the user may go into a withdrawal state. Conversely, if the potency is far above the accustomed level, the user can die from overdose. Heroin in street samples shows a wide variation in potency. Discrete doses may contain as little as 3% or as much as 90% heroin. Yet drug users often may not be aware of this: and even when they are, few are capable of checking a drug's potency.

Users' ignorance about the identity, purity, and potency of street drugs leads to greater and more frequent health-related problems than can be attributed to the pharmacological actions and effects of the drugs themselves. Overdose, life-threatening drug interactions, infections, and tissue damage are everyday results of users' not being able to depend on the reliability of the drugs available to them.

Laboratory Identification and Analysis of Drug Products

Law enforcement activities concerned with monitoring the distribution of illicit drugs have resulted in the development of the science of "pillistics." The punch-and-die sets employed in the production of tablets produce characteristic marks on the tablets that can be used to identify them in much the same way that rifling marks on bullets can be used to identify weapons.

However, the most satisfactory approach to identifying drugs with real certainty is a detailed, modern laboratory characterization of the actual drug substances. This approach is useful:

- whenever medical, community, or legal professionals or others concerned with drug abusers or drug-abuse situations need to know what drug substance has invaded their communities and has affected or may affect their clients;
- whenever it is necessary to determine what drug is involved in a case of drug poisoning so that proper therapeutic procedures can be instituted;
- whenever it is necessary to determine what substances were in a victim's body at time of death in order to assess what role these substances may have played in the death itself;
- whenever law enforcement agencies require a definitive characterization of a drug product so that they can monitor its distribution and criminal use.

Qualitative analysis involves identification of the drug substances present in the dosage form or body fluid presented for analysis and, in some cases, the nature of contaminants. The identification process often begins with establishing the class of drugs to which the sample belongs (e.g., narcotic analgesics), and only then focuses on the specific drug (e.g., heroin, as opposed to codeine or morphine). The process of qualitative analysis becomes more difficult if one has no idea of the nature of the substance to be analyzed. The systematic but laborious procedures available are often too time-consuming to be helpful especially in medical emergencies. Often a physician who needs an analysis for an immediate therapeutic decision is kept waiting because there is no local analytical laboratory which maintains an extensive collection of reference drug samples for purposes of comparison. In that situation the physician will engage in symptomatic treatment (maintaining breathing, monitoring body temperature, etc.) until recovery or until further information is available. In the absence of a satisfactory laboratory analysis, the physician may be able to obtain some useful information about the identity and quantity of the drug ingested by asking the patient or friends of the patient (although such information is subject to the limitations noted above) and by examining drug materials found in the patient's possession.

Qualitative analysis is further complicated by the fact that many drug preparations contain more than one drug; in such cases the component drugs of the sample must usually be separated before they can be identified. A further complication relates to the greater potency of some of the newer synthetic and semisynthetic compounds. As potency increases, the amount of drug present per unit dose decreases. Thus there may be only a minute amount of material available to analyze.

A wide range of analytical technologies are employed in this process. They range from classical color and crystal tests (which tend to be of low specificity and sensitivity), through paper, thin-layer, and gas-liquid chromatographic methods, spectrofluorometry, and infrared and ultraviolet spectrophotometry, to X-ray diffraction and mass spectrometry (the last often coupled to a gas-chromatograph/computer system).

While qualitative data establish only the identity of the drug or drugs present in the sample (and in some cases impurities and/or adjuvants), quantitative analysis establishes how much is present. Thus, quantitative analysis is often as important a tool as qualitative analysis. It permits assessment of the quantity of the drug present in the system at a specific time, and can therefore shed some light on the role of the drug in the event under investigation. In medical emergencies, given knowledge of the concentration of drug in plasma and of the usual plasma half-life of that drug, the physician can estimate the size of the original dose and the time it will take for the patient's drug level to be reduced to an inconsequential level.

Techniques which are widely used for quantitative analysis of drugs include several which are also used in qualitative analysis, notably ultraviolet spectrophotometry, colorimetry, and gas-liquid chromatography (the last often coupled to a mass-spectrometer/computer system). In addition, many classical colorimetric methods of quantitation continue to be used to some extent. Although thin-layer or paper chromatography is used primarily for separation and identification of drugs, new methods are being employed which involve the scanning of these chromatograms by various detectors which permit quantitation of the materials present.

DIFFERENT WAYS DRUGS CAN BE CLASSIFIED: METHODS/CATEGORIES OF DRUG CLASSIFICATION

As the number of drugs available to us increases along with ever greater detailed knowledge of their effects, it has become desirable to classify them in various ways, partly as a means of simplification when referring to them in special contexts and partly as a means of delineating and emphasizing the relationships between the properties of different drugs.

Each classification yields important information with respect to the source, function, or effect of a given drug. The different classifications reflect the distinctive needs of different scientific or social contexts. There are seven basic drug classifications.

1. *Classification by Origin*

Drugs derived from natural sources such as plants are often classified by source or origin. The term "opiate" is an example of classification by origin, the source of all true opiates being the latex of the opium poppy, *Papaver somniferum*. Yet, as this classification reflects only the source, it may include many compounds with diverse actions.

Opium, the dried latex from the poppy, contains a number of alkaloids, including morphine, its most potent analgesic constituent; papaverine, a smooth-muscle relaxant; and codeine, an effective antitussive (cough-suppressant) agent with essentially lower analgesic potency than morphine. All these drugs are referred to as opiates, with the term reflecting their common natural source. Frequently the source name is applied not only to these drugs but also to semisynthetic compounds such as heroin and to entirely synthetic compounds such as methadone or meperidine. However, some purists insist that the synthetic drugs, which are not actually obtained from opium but only mimic the effects of opium alkaloids, should be termed "opioids," or opiate-like drugs, and should not be referred to as opiates.

2. *Classification by Action Prototype*

This type of classification is generally used to compare a newly discovered or developed drug to an older drug, usually on the basis of similarity of overt effects as assessed by drug screening procedures. There are a number of standard drugs, such as atropine and amphetamine, against which the actions of other drugs can be compared. For example, tetrahydrocannabinol (THC), the major active principle of marijuana, is often described as having an atropine-like effect because, like atropine, it can speed up the heart and dry the mouth. In classification by prototype, marijuana or THC could therefore be listed under atropine-like drugs. Classification by prototype is generally an early designation which is discarded as soon as more specific information about the drug is known.

3. *Classification by Therapeutic Use*

Although classification of a drug by its therapeutic use is convenient for medical personnel, it often does not reflect accurately the nature of the nonmedical use and abuse of the drug. For example, amphetamine, a major drug of abuse, is often classified clinically as an anorexiant (appetite suppressant); yet its abuse is primarily based on its psychoactive stimulant effects. Similarly, morphine is commonly classified as a narcotic analgesic (pain killer); yet its considerable abuse arises from its effect as a euphoriant. Moreover, many drugs have more than one therapeutic use and must therefore be included in several therapeutic classes. Thus, preparations derived from opium are sometimes included in the class of antidiarrheal agents because of their efficacy in stopping diarrhea, or in the class of antitussive agents because of their efficacy in cough suppression.

Frequently, the therapeutic or medical use of a drug is dependent on an effect which is quite undesirable from the point of view of the nonmedical user. For example, while chronic users take narcotic analgesics in order to achieve euphoria, at the same time they frequently experience great discomfort from the constipating effect—the same effect for which the drugs are often prescribed in the treatment of moderate to severe diarrhea.

4. *Classification by Site of Drug Action*

Classification by site of action is of limited usefulness, for any one drug may have an effect on several different areas in the body. Cocaine, for example, has both CNS-stimulant effects and local-anesthetic properties; therefore, to categorize it as a CNS stimulant tells only one part of the story. In addition, several drugs chemically very different from each other and with markedly differing mechanisms of action and/or net effects may affect the same tissue. For example, the classification "CNS stimulant" is very general and covers such widely disparate drugs as cocaine, amphetamine, and strychnine.

5. *Classification by Chemical Structure*

Many purely synthetic compounds with no alternative natural source are classified by the chemical structure of the parent synthetic compound. The barbiturates are a good example of this type of classification: all drugs belonging to this group are named after the parent compound, barbituric acid, because they all share a common core structure. Pharmacological activity may vary both quantitatively and qualitatively within such a grouping, however. Barbituric acid, for example, unlike the barbiturates that derive from it, does not have sedative/hypnotic properties.

6. *Classification by Mechanism of Action*

This classification, which is based on an analysis of how the drug produces its effects, is the ideal method of classification, although it is the least used. The problem is that for most drugs we do not understand the mechanism of their action, although a major emphasis of current pharmacological research is the investigation of this area. One drug normally classified by mechanism of action is tranylcypromine (Parnate). From the mechanism perspective, this drug is classified as a monoamine oxidase (MAO) inhibitor—that is, a substance that renders the MAO system in the body less active. The MAO system works in the following way. Certain amines which occur as normal body constituents, as well as some which occur in everyday foods, must normally be destroyed by the MAO system. The amines in wine and aged cheese, for example, if not destroyed, can produce a severe and sometimes fatal hypertensive crisis. To classify tranylcypromine by its mechanism of action, therefore, is to underline to the physician some of the properties and risks associated with the drug and the need to instruct the patient carefully in the foods to be avoided.

This method of classification defines a profile of various drug activities some of which may be useful and others of which may be quite undesirable.[2]

7. *Classification by Street Name of Drug*

Nonmedical use of drugs has also given us a form of classification which emerges from the drug subculture and especially from the street drug market. The slang names coined in these environments reflect a variety of associations, as in the numerous names for marijuana—pot, weed, Mary Jane, etc. Sometimes, however, these names do indicate pharmacological effects. “Speed,” for example, is a reasonable description of the effect on the central nervous system of the stimulant drug methamphetamine. By a similar logic, sedative/hypnotic drugs are referred to as “downers.”

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[2] It is important to note that since there are variations from drug to drug within a class so defined—in potency, duration of action, and tissue distribution patterns—the clinical significance of the various drug activities will also vary.

Multiple Classification

Heroin is an example of a drug which can be classified in several ways, in accordance with the above headings. Under classification by origin, heroin is an opiate. Under chemical structure, it is of the morphine type. Under therapeutic use, it is a narcotic analgesic as well as an antidiarrheal agent. Under site of action, it can be classified as both a CNS depressant and a gastrointestinal drug. Under mechanism of action, however, there is no clear-cut classification, because the mechanism of action of heroin and other narcotic analgesics is not yet fully understood. Each classification reveals an important piece of information about the drug's impact. Even some street names suggest information about the drug's effect. For example, "smack" describes the sudden extremely intense physical sensation that heroin produces almost immediately after intravenous injection. Therefore, to understand fully the nature of the drug and its effects, it is useful to be familiar with all of the methods of classification.

METHODS OF NAMING LEGAL PHARMACEUTICALS

Considerable misunderstanding exists as a result of the many different drug-naming practices. Many drugs can be identified by a multiplicity of names, and understanding how these names are derived will help reduce confusion surrounding drug identification.

There are six types of names applied to drugs: chemical name, manufacturer's laboratory designation, chemical group name, nonproprietary/generic name, proprietary name, and general-use name.

The *chemical name* is the full, systematic chemical identification of the structure of a drug substance. It contains enough information to allow a trained chemist regardless of the language spoken to identify the drug unequivocally and (assuming skill and resources) to synthesize it. It is in effect a verbal blueprint of the drug's structure. For example, the chemical name of the minor tranquillizer diazepam is 7-chloro-1,3-dihydro-l-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. In many cases, however, the complete chemical structure is not known, particularly for drug preparations derived from plant and animal sources (e.g., hormones and enzymes). These latter types of drugs therefore receive highly technical biochemical, botanical, or zoological names, properly scientific and precise (although they do not unequivocally describe the drug's chemistry). Chemical names are, however, too long, complex, and unwieldy for common use.

The *manufacturer's laboratory designation* is usually a code name or a number given during the early stages of laboratory development and investigation—for example, RD 5-6901 for the sedative/hypnotic drug flurazepam (Dalmane). When a compound appears to be highly promising, its code name is discarded and a nonproprietary name is coined. In the case of diazepam, a well-known and established drug, the manufacturer's laboratory designation was long ago discarded. Occasionally, however, lab jargon or a chemical abbreviation is retained as a means of identifying certain drug substances—for example, ASA for acetylsalicylic acid, which is marketed by Sterling under the trade name Aspirin and by other manufacturers as ASA.

The *chemical group name* is the designation that applies to that group of drugs with similar chemical structure. Generally, drugs belonging to the same chemical group produce a spectrum of similar effects. The amphetamines would be an example of a chemical group.

Nonproprietary/generic names are short general names for a drug. They are used in the public domain in place of the more awkward, if more specific, chemical names. Like proprietary names, they reveal no useful information about the drug's nature or effects. Diazepam is the nonproprietary/generic name of the drug which is widely marketed as Valium or Vivol. Nonproprietary/generic names are not subject to trademark and can therefore be used to refer to products marketed by different manufacturers. The majority of the articles in sections 3, 4, and 5 of this book are titled by the drug's nonproprietary name.

The *proprietary (brand) name* is the one given by a particular manufacturer to its product. In the case of the benzodiazepine-type minor tranquillizer chlordiazepoxide, Hoffman-La Roche has given it the proprietary name Librium, while other manufacturers use the proprietary names Novopoxide and Solium. Proprietary names are trademark names and are always capitalized.

The *general-use name* may be identical with the nonproprietary name or the proprietary name, or it may represent a rough classification according to type of use. For example, phenobarbital, a barbiturate, might be called "sleeping pills" by those for whom it has been prescribed for that purpose and "downers" by street users valuing its euphoriant properties. In some cases a well-advertised proprietary name is used loosely to refer to all identical products; the name Aspirin, for example, is colloquially extended to other brands of ASA.

In Table 1, three drugs are listed under their various names and classifications; they are the well-known stimulant amphetamine, the minor tranquillizer diazepam, and the hallucinogen LSD.

TABLE 1

Names and Classifications of Three Drugs

	Amphetamine	*Diazepam*	*Lysergic Acid Diethylamide*
Chemical name	2-amino-1-phenylpropane (4-chlorophenoxy) acetate	7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one	N,N-diethyl-d-lysergamide
Manufacturer's laboratory designation	no longer in use	no longer in use	LSD-25
Chemical group name	amphetamine	benzodiazepine	indolealkylamine
Nonproprietary/generic name	dextroamphetamine	diazepam	lysergic acid diethylamide
Proprietary name	Dexedrine	Valium, Vivol (and others)	no longer in production—formerly Delysid
General-use name	dexie, dex, upper, amphetamine	trank, tranquillizer, downer	acid, LSD

DIFFERENT CHEMICAL FORMS IN WHICH DRUG DOSAGES CAN APPEAR

One of the complications of drug nomenclature arises from the fact that some drugs exist in more than one chemical form. For example, pentobarbital, a typical barbiturate sedative/hypnotic drug, has the chemical characteristics of a weak acid, and like other weak acids it is capable of reacting with bases to form salts. Thus pentobarbital in the presence of the base sodium hydroxide will form the salt sodium pentobarbital (or, as it is more usually described, pentobarbital sodium).[3] Both the "acid form" of the drug (pentobarbital) and the "salt form" of the drug, pentobarbital sodium or sodium pentobarbital, have the same pharmacological properties, although they differ in their physical properties (such as solubility in water, alcohol, or other organic solvents; melting point; some spectral characteristics; pH of aqueous solution). Therefore, in circumstances where it is useful to have the drug dissolve rapidly in water or gastric juice, its more water-soluble form (pentobarbital sodium) will be preferred. Because pentobarbital and pentobarbital sodium share the same pharmacological properties, both are generally referred to as pentobarbital, although pharmacists and chemists will emphasize the distinction between the two.

The majority of psychoactive drugs have the chemical characteristics of bases. That is to say, they are capable of reacting with acids to form salts. Thus morphine, in its "free base" form, will form a salt, morphine sulfate, in the presence of sulfuric acid. Similarly, a common salt of amphetamine is amphetamine sulfate. Many other psychoactive drugs are commonly available in the form of their salts produced by reaction of their "free base" form with hydrochloric acid. Although by analogy with the sulfate salts of morphine and amphetamine one would expect salts formed with hydrochloric acid to be called "chlorides," they are more commonly called "hydrochlorides."[4] Less commonly, some drugs are encountered as salts of other acids (e.g., the hydrobromide produced by reaction with hydrobromic acid, or the citrate produced by reaction with citric acid).

Drugs in their "free base" form are commonly oily materials which tend to be chemically unstable and difficult to crystallize. With crystalline forms it is easier to establish identity and purity, and the drug in crystalline form can be more accurately weighed for preparation of dosage forms. Most drugs are therefore commonly marketed in the form of a crystalline salt. The particular salt (hydrochloride, sulfate, citrate, etc.) in which a given drug is marketed is usually determined by the relative costs of production, chemical stability, phys-

[3] An analogous reaction is that of acetic acid (CH_3COOH) with sodium hydroxide ($NaOH$) to form sodium acetate (CH_3COONa).

[4] From the pharmacologist's viewpoint the more rapid dissolution of a salt after oral administration does not result in any significantly increased rate of drug absorption, although drugs in the free base form are more fat soluble than their respective salts and tend to penetrate the blood-brain barrier more quickly.

ical characteristics, etc. among the various salts which can be prepared. As was noted with respect to pentobarbital, common usage of drug names rarely distinguishes between the base (or acid) and salt forms of the drug because of the general identity of pharmacological properties, although pharmacists and chemists are vitally concerned with the more precise designations.

There is one context in which the precise drug form must be emphasized—where the question relates to drug dose and drug concentration in biological fluids. The form in which the drug is available (acid, base, or salt) is related to the size of the dose to be administered, for the molecular weight of each form is different. For example, the molecular weight of pentobarbital (in its "free acid" form) is 226.3, while that of pentobarbital sodium is 248.4; therefore, 226.3 mg of pentobarbital "free acid" has the same drug effect as 248.4 mg of pentobarbital sodium.

UNDERSTANDING DRUG EFFECTS

The intensity of a drug effect is governed by two major factors:

- the concentration of drug at the site of action in the body; and
- tolerance—the sensitivity of the target cells (i.e., the magnitude of their response to a given concentration of drug).

THE CONCENTRATION OF DRUG AT THE SITE OF ACTION

The concentration of drug at the site of action in the body at any given time after administration is determined by both the size of the dose and the pharmacokinetics of the substance (i.e., the way in which it is absorbed, distributed, metabolized, and excreted).

Absorption and Routes of Administration

The extent and rate of absorption of a substance depends on the chemical properties of the drug itself and the way in which it is administered. Drugs which are fat (lipid) soluble are best able to diffuse across all those membranes which consist of a double layer of complex protein-fat molecules called phospholipids. The fatty ends of these molecules are lined up facing each other to form a barrier that is virtually impenetrable to water-soluble (hydrophilic) substances. Therefore, all drugs that are absorbed across intestinal mucosa, the mucous membranes of the nose, throat, rectum, etc., or the membranes of the small air cells of the lung (alveoli) must be fat soluble in order to be absorbed at all.

The rate of absorption depends on the concentration of the drug, its degree of fat solubility, the surface area of absorption, and the diffusion distance (i.e., the number of membranes it must cross before it reaches the bloodstream).

There are four principal methods of drug administration: oral, across mucous membranes, by inhalation, and parenteral (injection). Each of these methods has its own advantages and drawbacks depending on the user's situation and on the characteristics of the specific drug. The choice is usually made on the basis of convenience, desired rapidity and duration of action, availability of sterile preparations, and the drug's solubility and absorbability. Following are brief descriptions of the different routes of administration with some of their attendant risks, benefits, and problems.

Oral (by swallowing): The oral route is the most common method of taking drugs. Oral dosage forms include capsules, tablets, liquids, and powders. Drugs taken orally are generally absorbed primarily in the small intestine rather than in the stomach.[5] However, drug absorption is sometimes affected by the presence of food in the digestive tract. Food can delay stomach emptying or it can dilute the concentration of a drug, thus delaying its absorption and reducing maximum possible drug blood levels. Furthermore, food can encapsulate the drug and allow it to pass out of the body in the feces without being absorbed.

Another characteristic of the oral route is the slowness with which the drug is absorbed into the bloodstream. Drug users looking for an immediate or intense effect or "rush" avoid the oral route.

The oral route is also ineffective with certain drugs because the stomach destroys them or turns them into a less effective drug. Heroin provides a good example of the latter phenomenon. It is degraded in the stomach into morphine, and once absorbed into the bloodstream, it passes through the liver before it can reach the brain. During its initial pass through the liver, so much of the morphine is destroyed that only a fraction of it ever reaches the brain. Therefore, oral ingestion of heroin is relatively inefficient.

[5] Because of the greater blood supply (which reduces the diffusion distance) and the greater surface area of the small intestine, diffusion occurs more rapidly there than in the stomach.

Absorption across Mucous Membranes: Mucous membranes form the moist surfaces that line the mouth, nose, eye sockets, throat, rectum, vagina, etc. As compared with the epidermis (skin), mucous membranes are thinner and have a greater blood supply and therefore a shorter diffusion distance. In addition, the cells of the mucous membrane lack keratin, a structural protein that reduces the permeability of skin. For these reasons, fat-soluble drugs are absorbed rapidly across the membranes of the mouth, nose, and rectum.

Certain drugs placed sublingually (under the tongue) are rapidly and effectively absorbed into the bloodstream. A group of drugs including nitroglycerin are taken sublingually for the treatment of angina pectoris (heart pains due to poor circulation of blood to the heart). Of those taken for nonmedical purposes, nicotine in the form of chewing tobacco is absorbed through the mucous membranes of the mouth. For a variety of reasons including taste, people do not commonly use the sublingual route for most drugs.

Sniffing (not to be confused with inhalation) allows a drug to be absorbed across the mucous membranes of the nose and sinus cavities. Examples of substances taken by sniffing ("snorting") are cocaine, amyl nitrite, and tobacco snuff. In the case of the first two, sniffing is the most effective way of getting the drug into the bloodstream. (Glue "sniffing" is actually an incorrect description; technically, glue and solvent vapors are inhaled and absorbed by the linings of the lung.) Most drugs cannot be effectively absorbed by sniffing, but for those which can,[6] this route is very rapid and effective. Irritating drug substances and those which interfere with blood flow may cause localized damage. Cocaine, for instance, is so physically disruptive that heavy users may perforate or entirely destroy their nasal septums and the lining of their noses.

Some drugs can be absorbed by the mucous membrane of the rectum. Rectal administration is sometimes chosen when oral administration would induce nausea and vomiting or when the patient is unconscious, a child, or otherwise noncompliant. The drugs are usually inserted in the form of suppositories. Examples of drugs that can be administered rectally are aminophylline, a drug used in the treatment of bronchial asthma and emphysema, and tribromoethanol, an anesthetic. There are many drugs, however, which cannot be absorbed effectively by these membranes. Moreover, since administration is unpleasant, this route is infrequent and unpopular.

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[6] Only those drugs which are very fat soluble are effectively absorbed by sniffing.

Inhalation: In the case of inhalation, the drug is absorbed into the bloodstream across the lining of the lung (i.e., the alveolar membrane). Since the surface of the lung is large and the diffusion distance is short, this is a very effective way to absorb certain drugs. For a drug to be inhaled, it must be either in gas form (e.g., the vapors of solvents), in fine liquid drops, or in fine particles of matter suspended in a gas (e.g., aerosols or the smoke from tobacco or cannabis). For many drugs, inhalation is the most rapid method of administration; its major drawback is that relatively small amounts of the drug can be absorbed at a single administration.

Parenteral (Injection): The term "parenteral" denotes those pathways through which drugs are injected directly into the body with a needle and syringe. There are three principal parenteral routes: subcutaneous, intramuscular, and intravenous.

Since normal barriers that protect the body from microorganisms (e.g., skin, mucous membranes) are bypassed by the parenteral routes, systemic infections may result from nonsterile needles and/or solution. However, substances need not be fat soluble for absorption.

Subcutaneous injection—commonly called "skin popping" by street users—involves injecting the drug under the skin. Of the three needle routes, it requires the least technical skill and is commonly used by beginners. The rate of absorption from the site of injection is slower than from intravenous injection but faster than from the oral route. A variety of drugs including heroin can be administered subcutaneously. If the drug and needle are not sterile, local or general infections may result. Furthermore, insoluble diluents tend to stay at the site of injection rather than enter the bloodstream. Both problems often lead to a tattooing of the skin and/or lesions or infections at the injection sites.

Compared to subcutaneous injection, intramuscular injection involves deeper penetration of the drug into the body tissue. The drug is injected directly into the muscle mass, where it is slowly absorbed into the bloodstream. Drugs injected may be either in solution or in suspension. Localized pain is a major drawback of intramuscular injection. Some drug abusers employ it because the needle can be inserted through the clothing. The risks of infection and of localized tissue damage are quite high.

Intravenous injection—popularly known as "mainlining"—involves the direct injection of the drug into the veins. It is one of the fastest ways of getting a drug into the bloodstream and also allows relatively large amounts of a drug to be administered at one time. Suspended particles may lead to the formation of clots, which may block blood vessels. If in a localized area, clots may lead to tissue damage; if in a vital area, such as the brain or heart, they may lead to death. Intravenous injection takes the drug into the superficial veins of the body. Some skill is needed to use this route effectively. For example, in order to find a good injection site, it is sometimes necessary to make the veins more visible by using a pressure cuff on the heart or "upstream" side of the site. The forearms and elbow-joint area are common sites for intravenous injection, although some users may avoid them so as to keep their drug use undetected. Since injection of drugs in high concentration irritates veins, eventually a frequently used vein becomes blocked and collapses, and another site must be found. A wide variety of sites on the body may be used, including the ankles, the scrotum, and the underside of the tongue. The needle marks on the body often indicate the duration and severity of the drug problem.

The Distribution of Drugs in the Body

Once a drug enters the body, it is absorbed into the bloodstream, which then distributes it throughout the body. The lymphatic system, composed of a network of glands and ducts, also plays a subsidiary role in the distribution of certain drugs.

The distribution of most drugs in the body is far from even; some drugs bind more strongly to blood elements, while others dissolve more readily in body fat, and a few have great affinity for bone tissue. Drugs must be highly fat soluble in order to enter the brain. The cells that line the cerebral capillaries, unlike those of most other capillaries, have no intercellular pores; therefore, the drugs must diffuse across the cell membranes. Similarly, fat-soluble drugs can cross the placental barrier of pregnant women to affect the fetus; these same drugs are also found in the milk of lactating women.

Unevenness of distribution is a barrier to the accurate interpretation of drug levels in blood; that is, it complicates efforts to find a correlation between blood levels and behavioral effects of a given drug. While it is generally the case that high drug blood levels are related to correspondingly greater behavioral effects than low levels, some drugs (notably the barbiturates) have passed their maximum blood level and are declining in concentration before the peak behavioral effects are seen.

In the case of alcohol, some of the above differences do not apply, since alcohol crosses all barriers to distribute uniformly in total body water. There is no selective binding of alcohol to any tissue. Therefore, in the nontolerant individual blood levels are correlated closely with behavioral effects. The same relations also hold for some gaseous anesthetics and solvents.

The Elimination of Drugs from the Body

Excretion: There are several routes by which drugs are excreted following their absorption and distribution. The following are some major organs involved in the excretory process:

In the human, the major route of elimination of most drugs is in the urine. The kidney acts as a pressure filter through which the blood passes. On its way through the kidney the blood is "filtered," and the filtrate or "primary urine" consists of a considerable amount of the blood's water together with all substances (including drugs) dissolved in this water. As the primary urine passes further through the kidney tubules, the kidney reabsorbs most of the water and some of the dissolved substances. Substances that are fat soluble tend to diffuse back into the bloodstream across the membrane of the kidney tubules. Obviously, then, the excretion of such compounds (a category that includes all unmetabolized psychoactive drugs) is inefficient.

The residual water and unreabsorbed substances constitute a more concentrated urine, which then passes from the kidney into the bladder and is eliminated in urination. In addition, some substances (e.g., some penicillins) are excreted directly into the concentrated urine.

The concentration of drugs and metabolites in the blood at the time of primary urine formation is reflected in the concentration of these elements in the urine. However, because of the process of reabsorption and active excretion in the tubules of the kidneys and the time lapse between primary urine formation and urination, it is difficult to use urine concentrations of drugs and drug metabolites as a base for accurate estimates of blood concentration of these substances. The drug concentrations determined in urine tests are therefore only a rough indication of blood levels.

It is possible to increase excretion of some drugs by altering urinary pH (for example, ASA is less fat soluble in alkaline urine, and therefore more easily excreted) or by administering diuretic drugs, which increase urine volume.

The intestines are a site of drug excretion as well as a site of drug absorption. Some drugs and drug metabolites have chemical characteristics which cause them to be actively secreted (or "pushed out") into bile as they pass through liver cells, and the drug-containing bile then empties into the intestines. Thus, these drugs and metabolites may be excreted in the feces. As is the case with the kidney, however, the net excretion by this route may be greatly reduced by subsequent reabsorption into the bloodstream of the fat-soluble compounds (including psychoactive drugs) further along in the intestines. In this instance, the drugs will go through the process of excretion all over again (enterohepatic cycling), and the drug effect may be prolonged.

Elimination of psychoactive substances by both the intestinal and renal (kidney) routes is thus often very inefficient. This factor explains the need for chemical changes that decrease fat solubility and hence reabsorption from the gut or kidney tubules. (See Metabolism, below.)

Volatile drugs (and volatile metabolites) such as solvents are commonly excreted in the breath. For very volatile substances, such as general anesthetics, the breath may be the major route of elimination. For substances such as beverage alcohol, it is a minor route. Nonetheless, it is possible through stimulation of breathing to increase the loss of the drug from the body. Since the amount excreted in the breath can be reliably related to the blood level, the concentration of alcohol in the breath, as measured by the Breathalyzer test,[7] serves to estimate the degree of intoxication.

All of the body's routes of elimination, including sweat and saliva (and in lactating women, milk), play a role in drug elimination. Though these are minor routes, they can be important in forensic analysis. They also sometimes have major consequences; for example, elimination of drugs via mother's milk means ingestion of drugs by infants.

Metabolism: Drugs are generally eliminated from the body in both changed and unchanged states: that is, part of the drug eliminated is chemically identical to that which was administered, and part has been chemically changed. The proportion of a drug dose eliminated in a particular state is determined by the nature of the drug, its dose, its route of administration, and the physiological characteristics of the user. As was pointed out in the discussion of excretion, the excretion of unchanged psychoactive drugs via the urine or feces is generally inefficient because of their high fat solubility. As a result, living organisms have evolved mechanisms for transforming fat-soluble substances into water-soluble breakdown products that can be readily excreted by the kidneys and/or the intestines.

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[7] See CNS Depressants chapter in section 2.

The process whereby a drug is changed to a different chemical state is called *drug metabolism* or *biotransformation*, and the new substances created by the process are called *drug metabolites*.

Drugs are biotransformed with the aid of specialized protein molecules called *enzymes*, which act as catalysts in the chemical reaction. Most drug metabolism occurs in the liver, although enzymes in the kidneys, gut, lung, and blood may also aid in the process. In the liver there are two types of enzymes: microsomal (insoluble) drug-metabolizing enzymes, and cytoplasmic (soluble) metabolizing enzymes (which metabolize alcohol and similar drugs).

The conversion of a fat-soluble drug to a substance that has sufficient water solubility for efficient excretion may involve several sequential chemical reactions, each step rendering the molecule slightly more water soluble than before. Thus many metabolites are often derived from the same parent drug (for example, there are at least 25 known metabolites from tetrahydrocannabinol, the main psychoactive ingredient of cannabis). Clearly, the process of biotransformation is very complex.

As the drug becomes progressively less fat soluble, it simultaneously loses its ability to cross the blood-brain barrier (i.e., to enter the brain) and hence loses its psychoactivity. For this reason, it was at one time believed that the purpose of the drug metabolism process was to detoxify the drug or make it less harmful to the human physiological system (hence the use of the obsolete term "detoxication"). Certainly many intermediary drug metabolites are less potent pharmacologically than the parent drug, and others are completely devoid of activity. However, some drug metabolites are pharmacologically quite active.[8] These produce the same sorts of pharmacological effects as the parent drug. For example, the minor tranquillizer diazepam is transformed to a large number of metabolites, including N-desmethyldiazepam,

[8] Mainly products of the first or second transformation that retain sufficient fat solubility.

[9] Occasionally, the parent drug is inactive and must be metabolized in order to become effective.

3-hydroxydiazepam, and oxazepam, all of which have pharmacological properties characteristic of the original drug.[9] Other drug metabolites can produce a completely different activity from the parent drug. As well, the metabolites of certain drugs may be even more toxic than the parent drug. Methanol (methyl alcohol) is an example of a drug metabolized to two very toxic metabolites, formaldehyde and formic acid. It is these metabolites which are considered responsible for disruption of the acid-base balance of the body and for damage to the optic nerve, both of which pose serious problems in cases of methanol poisoning.

Both types of liver enzymes, microsomal and cytoplasmic, are *inducible*—that is, repeated drug exposure causes them to increase in number; the result is a faster metabolic rate—that is, a more rapid conversion of the ingested drug into its metabolites. This speeding of the process can result in increased intensity and speed of onset of drug effects if the original substance was inactive and the metabolites active, or it can result in decreased intensity and duration of effect if the original drug was active and the metabolites inactive.

DRUG TOLERANCE: THE BODY'S ADAPTATION TO DRUGS

The magnitude of the body's response to a drug depends not only on its concentration at the site of action but also on the sensitivity of the target cells. This sensitivity is governed by innate (probably genetically controlled) factors and by adaptive changes which can occur in the body in response to chronic exposure to the drug substance. The result is often a progressive loss of sensitivity to the drug. The loss of sensitivity is called *tolerance* and can result from a variety of mechanisms. Tolerance is an adaptation which in turn influences drug-taking patterns and behaviors. Following is a brief review of the most important concepts in the area of tolerance and dependence.

Tolerance—Metabolic (Dispositional Tolerance)

A person who uses a psychoactive drug, usually wants the desired effect to last as long as possible. The process of drug metabolism or transformation limits the drug's duration of action. Moreover, for many drugs, repeated exposure of the drug-metabolizing system to a drug actually increases the metabolizing system's capability and efficiency; the result is that the drug is metabolized more quickly and the duration and intensity of the desired effect are considerably reduced. At this point a person is said to be *metabolically tolerant* to the drug's effects. To regain the effect, the person may try to increase both the dosage and frequency of administration. However, the returns in terms of effect are diminishing.

Cross-Tolerance—Metabolic (Dispositional Cross-Tolerance)

Metabolic cross-tolerance occurs when chronic treatment with one drug reduces the pharmacological effects of a second drug. The first drug, in the process of inducing its own increased metabolism, also induces the increased metabolism of a second drug. (For this phenomenon to happen, each of the drugs must be metabolized consecutively by the same enzymes in the liver.) Within the sedative/hypnotic drug class, many of the drugs are metabolized by the same enzymes. However, alcohol and the barbiturates do not produce metabolic cross-tolerance with each other, because they are metabolized by different enzymes in the liver.

Tolerance—Central Nervous System (Functional Tolerance)

Central nervous system (CNS) tolerance occurs when the brain or some part of it adapts in such a way as to diminish the effect that a given drug will have on the function of cells. CNS tolerance is characterized by differential development to different effects; that is to say, it does not develop at the same rate to different effects of a drug, and to some effects it may not develop at all. For instance, tolerance develops rapidly to certain CNS-depressant effects of sedative/hypnotics but very slowly to the respiratory-depressant effect. The difference has important consequences for the chronic sedative/hypnotic user. As the user increases the dose in order to overcome CNS tolerance and thus regain the psychoactive effect, tolerance to the respiratory-depressant effect increasingly lags behind. Eventually, the intoxicating dose may be high enough to cause respiratory arrest.

Cross-Tolerance—Central Nervous System (Functional Cross-Tolerance)

CNS cross-tolerance occurs when the user's brain, having become tolerant to the presence of one drug, invokes the same adaptive mechanisms when exposed to other drugs which produce similar psychoactive effects. For example, a chronic heavy user of alcohol, which is a sedative, will require a higher dose of general anesthetic for surgery than a nondrinker. Furthermore, once tolerance to a given level of alcohol is produced, the user will no longer experience the mood-altering properties of most other sedative/hypnotic drugs unless they are administered at higher than the equivalent dose level of alcohol to which tolerance has been achieved.

Frequently CNS cross-tolerance but not metabolic cross-tolerance develops between two drugs (such as alcohol and methaqualone). However, if either type of cross-tolerance develops between two drugs, the dose of either drug must be increased if it is to have any effect.

Tolerance—Tachyphylaxis

On chronic exposure, most psychoactive drugs produce tolerance of a type characterized by an increase in the amount of drug required to produce a certain intensity of effect. In other words, the maximum effects of the drug can still be elicited if the administered dose is high enough. Thus the user tends to increase both the dose of the drug and the frequency of its administration in order to experience the desired effects.

In the case of LSD and certain other hallucinogens, however, the development of CNS tolerance follows a different pattern. With these drugs, in contrast to other psychoactive drugs, there is a reduction in the maximum achievable effect no matter how great the dose. In fact, the effect may be reduced to zero. Repeated doses over as few as four days can produce absolute insensitivity, and an escalation of dose will not produce the expected psychoactive effects. The user must then abstain for several days in order to restore sensitivity. This phenomenon leads to a pattern of episodic use of LSD (e.g., "weekend tripping"). There is considerable cross-tachyphylaxis among LSD, mescaline, and psilocybin, so that a switch from one of these drugs to another will not compensate for the overall reduction of response.

DRUG DEPENDENCE

There are three commonly accepted definitions of drug dependence, reflecting different classes of effect:

1. Physical dependence is a state in which the body has adjusted to the presence of a drug, so that when the drug is withdrawn, there are clear physical withdrawal symptoms usually involving discomfort and pain. In extreme cases (and with certain drugs, such as barbiturates) the effects of rapid withdrawal can be life-threatening because the body has come to depend on the presence of the drug.
2. Psychological dependence is a state characterized by emotional and mental preoccupation with the drug's effects and by a persistent craving for it.

3. Drug dependence as defined by the World Health Organization is a state in which self-administered drugs produce damage to self and society. This definition may or may not involve the concepts of physical and psychological dependence.

Physical Dependence

With chronic use of certain drugs, the body of the user adapts to the increased levels of drug in the system (i.e., tolerance develops). The body is now used to the presence of the drug; if it is withdrawn, the body goes into a state of drug deprivation. Under this condition, withdrawal symptoms represent an unmasking of the body's adaptation to the drug's presence. Painful and sometimes dangerous withdrawal symptoms can then be seen to constitute the body's signal that it needs the drug to maintain itself at the adapted state of functioning. The body takes a certain period to adapt to a decreased level or to the absence of the drug. If the drug is withdrawn suddenly, the body may go into a state of crisis and the withdrawal symptoms can be intense. In some cases (e.g., with sedative/hypnotics) those symptoms represent a state of shock.

Symptoms of drug withdrawal tend to be the opposite of the effects produced by the presence of the drug in the body. For example, the effect of barbiturates on the body is sedation; the effect of withdrawal from barbiturates is hyperexcitability. For heavy users of barbiturates the levels of hyperexcitability produced by rapid withdrawal can be great enough to bring on fatal convulsions. In the case of amphetamines, the reverse is the pattern: the normal effect of amphetamines is excitation (stimulation), and a principal withdrawal effect is mild to severe emotional depression. The physical effects of amphetamine withdrawal are not life-threatening, although people have been known to commit suicide because of the psychological impact of the depressed state.

Longer-acting drugs tend to produce less intense withdrawal symptoms, for the body has more time to adapt to the decreasing presence of the drug.

Psychological Dependence

The term "psychological dependence" defines those apparently nonphysical symptoms that occur on termination of drug exposure. Craving for a drug is the most common withdrawal symptom of psychological dependence and is also believed to be a major factor governing the continued self-administration of psychoactive drugs. It had been thought previously that certain other mild effects attendant upon drug withdrawal were of psychological origin (e.g., sleep disturbance and irritability). These symptoms are now widely thought to be based on protracted subclinical physical withdrawal reactions. They are therefore more properly thought of as subtle manifestations of physical dependence.

Psychological dependence is ordinarily manifested in the form of compulsive drug-taking habits, but the frequency and pattern of habit can differ considerably from one individual to another.

Addiction

The term "addiction" refers to dependent patterns of drug self-administration without making a distinction between psychological and physical dependence. Traditionally it carries with it the idea of moral weakness. In order to overcome the moral overtones and vagueness of meaning, the World Health Organization proposed that the word be replaced by the term "drug dependence." It is still customary, however, to refer to the "addiction liability" of a drug, by which is meant the propensity of a drug to produce psychological or physical dependence in those who use it. In this book, the term has been replaced by "dependence liability."

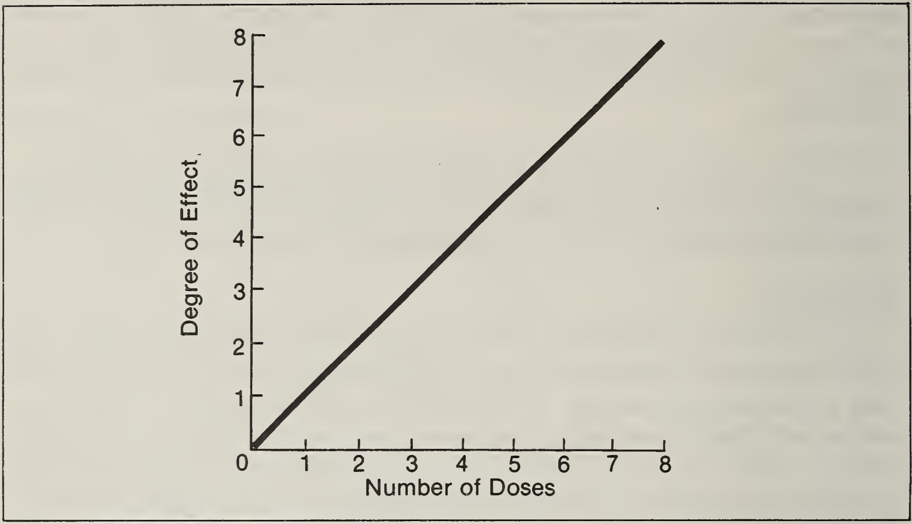
QUALITATIVE AND QUANTITATIVE DRUG ACTIONS AND INTERACTIONS: GRADATIONS IN THE PHARMACOLOGICAL EFFECTS OF PSYCHOACTIVE DRUGS

Anyone who is naive about the effects of psychoactive drugs might assume that doubling the dose of a drug would double its effect, tripling the dose would triple its effect, and so on. This expectation of the relation of dose to effect would be as shown in figure 1.

That the actual relationship of dose to effect is not so simple is a fact that most North Americans are sufficiently sophisticated to appreciate. Their experience, for example, has led them to recognize that although an initial drink may have little observable effect on their bodies,[10] the next few drinks are likely to have a much greater effect. This understanding reflects the fact that there is a threshold perhaps not yet reached by a small dose of a drug; however, once that threshold has been crossed, each subsequent dose creates a greater effect up to a

[10] Unless they are drinking on an empty stomach.

FIGURE 1



certain upper limit or ceiling. To develop this concept graphically, the pharmacologist plots drug effects against the logarithm of the number of doses (or the size of dose) to obtain a log dose response curve which is S-shaped (sigmoidal); figure 2 illustrates this curve and the concepts of prethreshold dose and ceiling dose, as well as the dose range where the effects of the drug rise very rapidly.

In the case of alcohol, effects that might be measured could include motor incoordination, emotional disinhibition, and impairment of judgment. For any psychoactive drug, a log dose response curve could be drawn, the exact characteristics of the curve varying with the individual drug, the route of administration, the particular drug effect being considered, and the degree of tolerance of the user. Figure 3 is a graph on which the dose response curves of barbiturates are described for a given population of nontolerant subjects with respect to two effects: sedation and anesthesia.

It can be seen from figure 3 that generally sedation is experienced at lower dose levels than are required to produce anesthesia. However, there is a dose level where some people are still only experiencing sedation while others are already beginning to experience anesthesia. Here we encounter another important consideration: namely, individual susceptibility to a drug's effects. A second illustration of this phenomenon

FIGURE 2

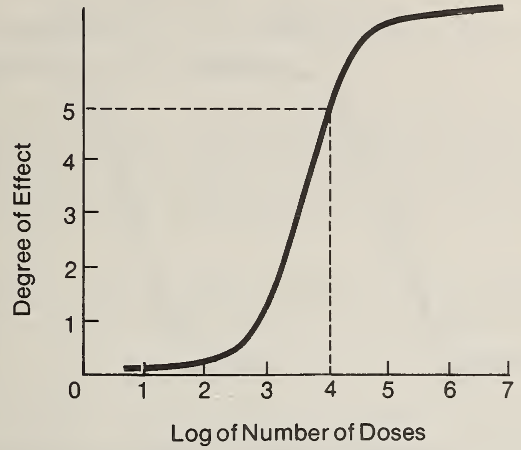


FIGURE 3

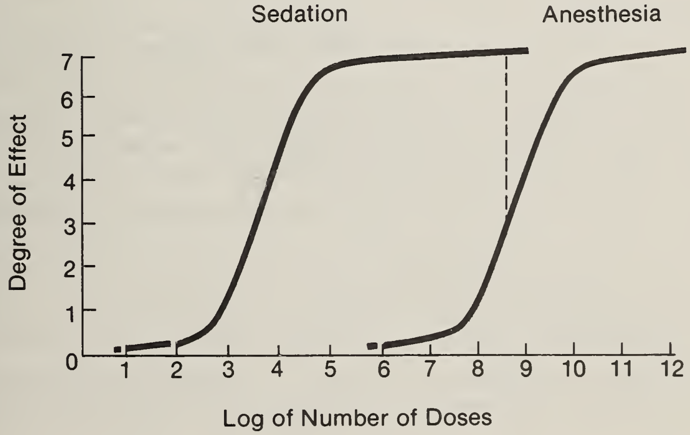
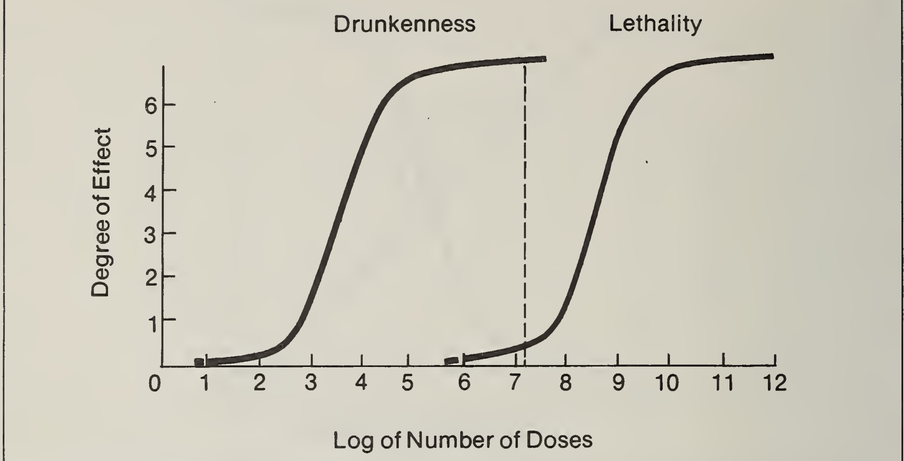


FIGURE 4



is the plotting of the dose response curve for alcohol with respect to drunkenness and lethality (figure 4). On this graph, there is a point at which some people will be walking around in a state of intoxication while others will have died, likely as a result of alcohol-induced respiratory arrest.[11]

Multiple Drug Use

Problems in predicting drug effects arise when someone ingests two or more different drugs which are interactive in their effects. For example, alcohol interacts with barbiturates, other sedative/hypnotics, or antihistamines predominantly through their common depressant effects upon the central nervous system. Users who at one time have taken one drink of alcohol and experienced almost no psychoactive effect, and at another time have taken an antihistamine and experienced only a very mild relaxant effect, may very well take one drink and one dose of antihistamine close together on a third occasion expecting the drug combination to have no marked effect on their system. If a user gets behind the wheel of a car under the influence of this combination, an accident could result. The user is not aware that a drug interaction known as *addition* is at work. Both alcohol and the other drugs mentioned above have depressant effects on the central nervous system, with the result that one drink of alcohol plus one equivalent dose of one of these other drugs, taken in a given period of time, will have approximately the same CNS-depressant effect as two drinks of alcohol taken in a similar period.

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[11] The above explanation of gradation of effects applies not only for the effects of a single drug dose but to the identical (or very similar) effects of different drugs taken the same time.

As another example, amphetamines and cocaine are both CNS stimulants; therefore, the effect of one dose of amphetamine combined with one equivalent dose of cocaine will be much more intense than the effect of a single dose of either drug alone.

There are, however, some aspects of drug interaction or joint action which complicate the clinical picture. Note, for example, the following:

Qualitative Changes: Drug users may experiment with two different types of psychoactive drugs in order to experience a spectrum of effects simultaneously that neither drug could produce by itself. A simple example would be to take LSD and an amphetamine in order to experience an amphetamine "high" while experiencing the perceptual distortions created by LSD. Others might take "downers" such as tranquillizers along with LSD in order to obtain a more quiescent psychedelic experience. In a therapeutic situation, those taking aminophylline for asthmatic attacks might also take tranquillizers in order to reduce the nervousness and irritability that the former drug can sometimes produce. Limited scientific information exists on the behavioral consequences of most such combinations.

Quantitative Changes (Changes in Degree of Effect): There are two kinds of quantitative effects produced as a result of drug interactions; these take place within (1) the pharmacokinetic context and (2) the pharmacodynamic context.

Pharmacokinetic considerations relate to the ways in which the presence of one drug in the body or past exposure to it influence the way that the body will handle a second drug. For example, one drug can block the metabolism of another; in a different combination, one drug may increase the absorption of another. Beverage alcohol interacts with methyl alcohol pharmacokinetically in that the former interferes with the metabolism of the latter; thus, perhaps surprisingly, a physician can treat a patient who has drunk a large amount of methyl alcohol by administering a large amount of beverage alcohol. The metabolism of the methyl alcohol will be slowed down, and indeed with luck most of the methyl alcohol may be excreted from the body unmetabolized in the urine and breath. The addition of the beverage alcohol will prolong the drunkenness but will avert the more serious effect of formaldehyde and formic acid poisoning. Another example of a pharmacokinetic drug interaction is that between beverage alcohol and the minor tranquillizer meprobamate. Alcohol speeds up the dissolving of meprobamate in the stomach, thereby increasing the rate of its absorption. The consequences can be serious if sufficient doses of both have been ingested to produce a significant depressant effect on the central and autonomic nervous systems.

Pharmacodynamic considerations relate to the ways in which two or more drugs interact in their effect on a common physiological system. Such interactions obviously will occur when the mechanism of action of the two drugs is the same. However, they may also occur when the mechanisms of action are different. For example, while both nicotine and amphetamine lead to increased blood pressure, they act on both different and common sites. Nicotine affects blood pressure through a complex of pharmacological actions including constriction of blood vessels and the release of a hormone, norepinephrine, from the adrenal medulla. This hormone directly stimulates the heart, increasing heart rate and raising blood pressure. Amphetamine raises blood pressure by the constriction of blood vessels and by both direct and indirect stimulation of the heart. The indirect stimulation is as a result of the release of the same hormone, norepinephrine, which in turn stimulates the heart; the direct stimulation is a result of amphetamine's action on the adrenergic receptors which are found in the heart tissue and mediate heart action. Thus, the net effect of the interaction of these drugs on blood pressure will be greater than when either drug is taken alone.

The magnitude of the combination of drug effects may, however, be restricted by the physiological system. In some instances, the effect of a combination of two drugs may be less than predicted because the system affected has reached its maximal response or because a counterbalancing mechanism has come into play. An example of the latter would be that increased blood pressure from increased heart rate may be partially compensated for by constriction of blood vessels in other parts of the body.

Vocabulary of Quantitative Effects

A clear definition at this point of certain terms as they are commonly used by pharmacologists will permit a more precise understanding of various types of drug interactions.

Synergism: This term has two widely accepted meanings in the drug context. Some people use it as a general term referring to any type of drug interaction without regard to the type of interaction. Others use the term as a synonym for potentiation. It would probably be most useful to retain "synergism" as a general term referring to any enhancing drug interaction.

Addition: The term "addition" refers to a drug interaction in which the identical (or very similar) effects of two different drugs combine to produce an intensified response. Response to the combined effect may be greater than the user expects, because the combined dose may raise the drug blood level above the maximum prethreshold level (as represented by a log dose response curve for the given effect). In this case, the additional degree of effect is not to be confused with potentiation. The term "addition" takes into account the log dose response for both drugs acting in concert. Alcohol and antihistamines taken together can produce an additive effect, as noted above.

Potentiation: A pharmacologist using the term "potentiation" is referring to a greater effect than could be accounted for by reference to the dose response curves of both drugs considered additively. The extra degree of effect could have many different biological explanations, including the inhibition of metabolism. An example of potentiation would be the sometimes substantial CNS-depressant effects that occur when diazepam (e.g., Valium) is taken in combination with such other CNS depressants as alcohol.

However, there is still some disagreement as to whether addition or potentiation is occurring in specific instances; both the degree and type of drug interaction will depend on a variety of factors including dose, schedule of administration, and tolerance.

Antagonism: By "antagonism" the pharmacologist is referring to an effect whereby the taking of a second drug (the antagonist) in sufficient doses will result in a dimunition of the net drug effect so that it is less than that associated with the response curve for the first drug (the agonist). The second drug cancels out some or all of the expected effects of the first drug. For example, the narcotic analgesic antagonist naloxone greatly reduces or cancels the effects of narcotic analgesics when it is taken in conjunction with them or shortly before or after.

ABUSE POTENTIAL

"Abuse potential" is a concept used in this book which involves three main variables—the intrinsic dependence liability of a drug (i.e., its propensity to produce dependence), the availability of the drug within society, and its inherent harmfulness with respect to the direct physical and psychological effects it produces in the user. The actual abuse potential of any given drug will depend on the degree to which these various factors interact to promote or limit widespread abuse.

Dependence Liability

The tendency to produce physical and psychological dependence varies from one drug to another and depends on three factors: the pharmacological nature of the specific drug, the route by which it is administered, and the amount of the drug used.[12]

Nature of the Drug: Both animal and human experiments have shown that drugs are natural reinforcers in much the same way as food, water, and sex. That is to say, it is the pleasurable effects produced by a drug that increase the probability that it will be taken again. Drugs vary dramatically in their intrinsic reinforcing properties. For example, heroin and cocaine, which produce intensely pleasurable effects, have a very high intrinsic dependence liability, whereas minor tranquillizers (e.g., diazepam) have much less intensely pleasurable properties and, as a result, a significantly lower intrinsic dependence liability.

A strong concordance exists in the findings of human and animal experiments designed to determine a drug's intrinsic dependence liability. Animals generally appear to find psychoactive drugs reinforcing to the same degree that humans do and tend to prefer the same drugs that humans prefer. For example, the highly addictive nature of cocaine in humans is reflected in the preference of animals for this drug. Cocaine has such intense reinforcing properties that animals will prefer it even when food, water, and sex are available as alternatives and even when exercising their preference leads to death. Because of this human/animal congruence of response, animals are used in drug-screening procedures to ensure that new substances being considered for release as legitimate therapeutic agents do not have an unacceptably high dependence liability.

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[12] Of course, individual susceptibility is also a factor in both physical and psychological dependence.

Route of Administration: Drugs which are administered by routes that produce rapid effects are more abusable than those which can be taken only by the slower routes. For example, drugs which are taken by sniffing, inhalation, or intravenous injection are generally more abusable than those of equal intrinsic dependence liability which are taken orally, for the former routes allow for more rapid and intense gratification.

Amount Used: For any psychoactive drug which can produce intense gratification, the probability of developing dependence increases correspondingly with an increase in the frequency of administration and the size of dose used. This factor is limited, however, by the tendency of psychoactive drugs to produce tolerance to their own effects with regular use.[13]

With alcohol, for example, occasional consumption involving low to moderate amounts is unlikely to create a state of dependence in the user. On the other hand, frequent high-dose use of alcohol greatly increases the probability of dependence.

Availability of the Drug in Society

Availability within society at large is a major factor determining the level of use/abuse of psychoactive drugs; the more widespread and abundant the supply, the more they are likely to be abused. Alcohol, which has only moderate intrinsic dependence liability, is nonetheless the most highly abused psychoactive substance in our society in large part because of its widespread availability. By contrast, heroin, which has very high intrinsic dependence liability, has traditionally posed a low overall social risk in North American society because of the restrictions placed on its availability. Legislation and law enforcement activity severely curtail its legal and illegal manufacture, possession, distribution, and importation. Here we see underlined the powerful social impact of availability: the more available a psychoactive drug is, the greater will be the number of people using it at higher dose levels. Therefore, it often becomes necessary to restrict access to a drug of even low to medium dependence liability.

Inherent Harmfulness

Inherent harmfulness or “toxicity” refers to the noxious or even lethal effects which a drug has the potential to produce. If this factor is perceived to be great enough, it will deter widespread use of the drug even if it is widely available and can produce desirable effects in addition to its toxic effects.[14]

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[13] See discussion of tolerance earlier in this section.

Methyl alcohol (methanol) and isopropyl alcohol (isopropanol) are two examples of drugs which are widely available and which can produce inebriating effects similar to those produced by ethyl alcohol (ethanol, beverage alcohol). However, both have a high degree of toxicity. Methyl alcohol causes blindness and death when consumed in any but the very smallest amounts; isopropyl alcohol (often found in rubbing compounds and other nondrinkable commercial products) is thought to produce severe liver and kidney impairment when consumed regularly in very small amounts, and in higher doses it too causes death. However, since both are known to have a very high degree of inherent harmfulness, they have a very low abuse potential.

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[14] The determination of which effects should be considered toxic is somewhat arbitrary and in part depends on the viewpoint of the observer. Obviously, drug-induced carcinogenesis (e.g., lung cancer) would be considered toxic by virtually everybody. On the other hand, a cannabis-induced "high" might be desirable to the adolescent user, but the disruption of short-term memory and concentration that occurs as part of the intoxication would be thought of as harmful by the user's teacher.

Section 2

Drug Classes

Central Nervous System (CNS) Depressants

Central nervous system depressants will be discussed in this chapter under two headings:

I. Sedative/Hypnotics

II. Minor Tranquillizers

The sedative/hypnotics, which comprise a broad range of substances, will be discussed first in full, and the minor tranquillizers will be treated at the end of the chapter.

I. SEDATIVE/HYPNOTICS

See the articles in section 3 on the following substances: ethyl (beverage) alcohol, barbiturates, benzodiazepines II (sedative/hypnotics—e.g., Dalmane), glutethimide (Doriden), inhalants (e.g., industrial and chemical solvents and aerosols), and methaqualone (e.g., Seladone). See section 4 for articles on chloral hydrate, ethchlorvynol (Placidyl), and methyprylon (Noludar).

The sedative/hypnotics are a chemically heterogeneous group of substances which cause depression of the functions of the brain and other parts of the central nervous system.[1] They include beverage alcohol (ethyl alcohol) and most sleeping pills/sedatives, the most important of which are the barbiturates.[2] Although not generally recognized as sedative/hypnotics, many industrial and commercial solvents, as well as certain aerosol propellants, produce a similar range of effects when inhaled.

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[1] Here, depression refers to a slowing/reduction in function rather than to mood or emotional depression.

[2] Certain over-the-counter sleep aids contain antihistamines or other substances which are not classified as sedative/hypnotics but produce drowsiness and sedation as side effects to their main actions.

Depending on the size of the dose, the effects produced by sedative/hypnotics range from mild sedation and hypnosis (i.e., sleep induction) to general anesthesia and in severe overdose death from respiratory arrest. Usually, these drugs are abused for their pleasurably intoxicating and inhibition-releasing properties; however, sleeping pills are also frequently abused by patients who independently increase the daily dose to compensate for rapidly acquired tolerance to the soporific effects. In fact, there is now a growing body of evidence indicating that after an initial period of frequent use, the barbiturates and newer sedative/hypnotics rapidly lose their therapeutic value in combating insomnia. For several reasons, to be discussed below, chronic use may even prove to be harmful.

Abuse of drugs in this class poses some of the greatest drug-related health, social, and legal problems in Western society.

HISTORY OF USE

Beverage Alcohol

The oldest sedative/hypnotic known to man is ethyl alcohol. The use of fermented alcoholic beverages dates back to at least 6400 B.C., when beer and berry wine were introduced; indeed, some historians trace alcohol use even further back in time to 8000 B.C., when the alcohol-containing beverage mead was prepared from honey. The date of the discovery of distillation remains uncertain; however, many experts believe the process was used in Arabia in about 800 B.C. The word "alcohol" is derived from an Arabic word meaning "finely divided spirit," and originally it referred to that part of the wine collected through distillation—the essence of wine. References to distillation at about the same time in China and India have also been found.

Brewing and wine-making are based on the biochemical process called fermentation. Undoubtedly the earliest fermented beverages were accidental discoveries. Fermentation occurs when certain kinds of yeast act on sugar in the presence of water, with the yeast deriving energy from the sugar by converting it into ethyl alcohol. Thus, alcohol is actually a waste product of yeast, and like all living organisms, yeast has a limited tolerance for its own waste. When the alcohol concentration is about 15%, fermentation stops. Another factor which limits the concentration of alcohol is the availability of sugar; that is, smaller amounts of sugar in the initial solution produce lower concentrations of alcohol.

Distillation is the process whereby higher alcohol concentrations can be obtained than can be reached by fermentation. Alcohol has a boiling point of 78.3 degrees and water 100 degrees on the Celsius scale. The mixture containing the two is heated, and the vapors are then collected and condensed into liquid again. Because of the difference in boiling points, a greater proportion of the alcohol from the original mixture crosses to the resultant liquid. Repeating the process tends to bring the liquid even closer to 100% alcohol, although modern distilled beverages are usually diluted to a concentration of alcohol which is substantially less than 100%.

Proof scales are widely used measures of alcohol concentration in various beverages.[3] The two widely used modern proof scales, the American and British, differ in certain respects. The U.S. proof strength (also used in Canada) is twice the percentage of alcohol in the beverage. Absolute alcohol, by this measure, is 200 proof, and a distilled spirit which is 40% alcohol by volume is 80 proof. In the more involved British system, 100 proof is 57.15% alcohol by volume at 15.6 degrees Celsius, and concentrations are expressed as degrees over and under proof.

Alcohol has become one of man's most popular and widely used psychoactive drugs, and it has formed an important role in the social behaviors of most cultural groups, although some (such as the followers of Islam) expressly forbid its consumption. Traditionally, it has been used for three major purposes:

- in medicinal use, as an anesthetic and for its sedating and sleep-inducing properties;
- for religious and other social celebratory occasions and rites, including sacramental use among Christians and Jews; and
- for recreation.

With regard to the last, virtually all cultures which have permitted recreational use of alcohol have also recognized the potentially harmful (and even hazardous) effects of heavy acute and chronic consumption.

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[3] The term "proof" is believed to originate from a rough test used until the 17th century to determine the quantity of alcohol in a given liquid. Gunpowder and a sample of the liquid alleged to contain alcohol were mixed and fire applied. If the liquid contained a sufficient proportion of alcohol, the powder would ignite. Thus, gunpowder ignition was "proof" of the alcohol content.

Accordingly, each has developed its own complex pattern of social and legal sanctions to be applied against the alcohol abuser.

Other Early Sedative/Hypnotic Drugs

Until the 19th century, ethyl alcohol was the only sedative/hypnotic drug in existence. Thereafter, several drugs with sedative/hypnotic properties were introduced into clinical medicine. Two of these, paraldehyde (1882) and chloral hydrate (1869), are chemical derivatives of aldehydes. Paraldehyde is a polymer of acetaldehyde, a product of the oxidation of ethyl alcohol. Paraldehyde was considered to be an exceptionally safe sedative/hypnotic for many years; however, it is now recognized to give rise to tolerance and dependence. It also tends to decompose when stored, and if then consumed, the resultant products of decomposition induce a clinically complex and difficult-to-manage state of intoxication. Paraldehyde also tastes unpleasant and leaves a disagreeable breath odor. For these reasons it is now rarely used.

Chloral hydrate is a substance formed by the chemical reaction of trichloroacetaldehyde (chloral) with water; it was introduced because it was believed to release chloroform slowly in the body. While the hypothesis was subsequently found to be incorrect, chloral hydrate did produce satisfactory sedative/hypnotic effects. Nonetheless, it too presented tolerance and dependence problems and caused gastrointestinal irritation in a number of users. Although the medical use of chloral hydrate rapidly declined after the introduction of the barbiturates, it appears to have regained favor among some clinicians. Its recent return to popularity seems to have resulted from the recognition that it possesses several advantages over many other widely used members of this class of drugs:

- chloral hydrate produces less "hangover" effect than most other common sedative/hypnotics;
- it appears to affect REM sleep less negatively;[4]
- in sleep-inducing doses, chloral hydrate produces little or no respiratory depression; and
- its propensity to produce physical dependence appears to be less than that of most other sedative/hypnotics.

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[4] Rapid eye movement sleep, an essential component of normal sleep, will be discussed in detail later in this chapter.

Bromides[5] were introduced to clinical medicine in 1857 originally to manage the symptoms of epilepsy. The treatment was based on a rather curious assumption. At that time, it was widely believed that some forms of epilepsy were caused by masturbation. Because it was also believed that potassium bromide acted as an anaphrodisiac (i.e., reduced sexual drive), many clinicians reasoned that this substance should indirectly reduce the occurrence of seizures by suppressing sexual appetite. In fact, bromides were found to control certain types of seizures effectively, but rather because they generally depress CNS functioning. They also proved to be useful as sedatives and hypnotics. Until the middle of the 20th century they enjoyed very widespread use for all of these purposes. Unfortunately, however, the chronic use of bromides often produces serious side effects. Because they are slowly metabolized and excreted, bromides accumulate in the body and eventually give rise to a toxic state known as bromism; the syndrome is characterized by mental and neurological aberrations, a skin rash which can cover the entire body, and gastrointestinal disturbances. These medications have now been larely replaced by other effective agents that are less toxic at therapeutic dose levels.

Barbiturates and Newer Sedative/Hypnotics

After the rapid advances in organic chemistry in the late 19th century, it was possible to synthesize an enormous number of new drugs. In 1903, the first barbiturate, barbital, was introduced and marketed under the trade name Veronal. To this day, members of the barbiturate family are among the most commonly used sedative/hypnotic agents.[6] Barbituric acid, the parent compound of the barbiturates, is a condensation product of malonic acid and urea. Although barbituric acid itself lacks sedative/hypnotic properties, there are many psychoactive derivatives which represent slight variations of the chemical structure of barbituric acid.

Barbiturates are prescribed for sedation, induction of sleep, anesthesia, and the management of certain types of epileptic seizures. Although once widely thought to be safe, barbiturates are now

[5] The bromides have been marketed in the form of their inorganic salts: sodium, potassium, and ammonium bromide.

[6] Although their popularity has recently begun to decline. It is likely that barbituric acid was named after Saint Barbara to mark its discovery on that saint's day. However, an alternative and colorful theory proposes that its discoverer, von Baeyer, named it after a Munich barmaid.

recognized to possess several significant liabilities. Chief among these are the depression of the respiratory control centres in the brain, the rapid production of tolerance as well as of physical and psychological dependence, and the potentially life-threatening effects of sudden unsupervised withdrawal. These problems have prompted the search for new sedative/hypnotic compounds which might prove to be safer. While the result has been a number of new compounds with similar sedative/hypnotic effects (methaqualone, glutethimide, etc.), most of these do not represent any significant advance in terms of the inherent liabilities posed by the barbiturates.[7] Each time one of these new drugs was initially marketed, researchers and practitioners claimed that it was effective and generally did not possess the degree of harmfulness ascribed to barbiturates. Unfortunately, these endorsements proved to be premature. However, flurazepam (e.g., Dalmane), a member of the benzodiazepine family of drugs,[8] appears to be as potent as the barbiturates and the newer sedative/hypnotics in its ability to induce sleep. Furthermore, after over 15 years of clinical use, there is now substantial evidence that flurazepam does not possess the serious drawbacks of the other sedative/hypnotic drugs.

SEDATIVE/HYPNOTIC ACTIONS AND MEDICAL USES

All sedative/hypnotic drugs can produce a spectrum of CNS-depressant effects ranging from mild sedation and relaxation to anesthesia, coma, and death from respiratory arrest. However, the doses necessary to produce a given effect vary greatly from one drug to another within this class. For example, for most people, 50 mg of a potent barbiturate such as butabarbital is sufficient to induce sleep, while the typical amount of chloral hydrate or glutethimide necessary to produce essentially the same result is tenfold greater, and for ethyl alcohol greater again. Furthermore, since many of these substances also produce harmful (or even hazardous) effects at doses required to produce anesthesia, they are a very poor choice for this purpose. In the past, ethyl alcohol was widely used as an anesthetic; however, doses necessary to produce anesthesia also produce dangerous and uncontrollable depression of those brain centres responsible for respiration

[7] Four important examples of these newer drugs are glutethimide (Doriden), methyprylon (Noludar), methaqualone (e.g., Triador) and ethchlorvynol (Placidyl).

[8] This family includes such widely used tranquillizers as diazepam (e.g., Valium) and chlordiazepoxide (e.g., Librium), and a newly marketed drug, triazolam (e.g., Halcion), used essentially for the same purposes as flurazepam (i.e., sleep induction).

and circulation, unpredictable involuntary muscle movements, and in some individuals erratic and possibly highly aggressive behavior.

There is also a broad range of durations of action among sedative/hypnotics.[9] In fact, barbiturates traditionally have been divided into subgroups based on differences in duration of action and prescribed (in appropriate doses) for different purposes accordingly: the ultrashort-acting agents (e.g., thiopental sodium) for induction of anesthesia; the short- and intermediate-acting agents (e.g., secobarbital sodium and amobarbital sodium respectively) for induction of sleep and sometimes sedation; and the long-acting agents (e.g., phenobarbital sodium) for sedation and for control of certain types of epileptic seizures. However, while many physicians continue to prescribe barbiturates according to their duration-of-action subgroupings, recent pharmacological research casts doubt upon the validity of this system of classification. It is now recognized that the elimination half-life of many of these drugs does not necessarily correspond to their duration of action, and that there appears to be enormous variation among users with regard to the half-life elimination of a given barbiturate. For example, the half-life elimination of a single sleep-inducing dose of amobarbital can range between 8 and 42 hours; therefore, the residual effects of a single dose may continue to be experienced by a few people for more than a day. (In the case of long-acting barbiturates, the aftereffects may linger for several days.) Furthermore, day-to-day use can result in an accumulation of the drug in the body. The accumulation will likely increase the rate at which the body acquires tolerance to the desired actions of amobarbital and may very possibly give rise to its abuse.

Except for hexobarbital, which tends to be completely eliminated within 24 hours, essentially the same consequences are possible with any other common barbiturate. Among other commonly prescribed sleep-inducing drugs, the elimination half-lives of methaqualone and of the psychoactive metabolites of flurazepam can extend well beyond 24 hours. (This is one of the few drawbacks of the latter drug.)

Effects of Subhypnotic Doses (Low Doses)[10]

In a drug-free state of wakefulness, the brain receives a constant barrage of stimuli from the environment; normally, these stimuli generate a level of excitation which we associate with alertness. More intense or greater numbers of stimuli produce uncomfortable levels of excitation which we usually experience as anxiety or tension. At low doses, sedative/hypnotic drugs raise the threshold for normal stimulation so that fewer stimuli get through to the higher brain centres, and those that do are reduced in intensity. The result is reduced levels of excitation and alertness, which we experience as relaxation or sedation. Unfortunately, however, sedative/hypnotics lack specificity in that it is hard to control for the desired effect. Furthermore, a number of side effects can simultaneously occur, for even at relatively low doses these drugs tend to produce general, although mild, depression of CNS functioning. The most common symptoms are drowsiness, mild to moderate motor incoordination, and some clouding of mental functions. Low-dose symptoms can also be affected by setting and user expectations, particularly the user's reason for taking a sedative/hypnotic drug. For example, an anxious psychiatric patient taking a typical sedative dose of secobarbital will experience relief from anxiety, possibly accompanied by drowsiness. On the other hand, a normal person taking a sedative dose of alcohol equivalent to the secobarbital (a few ounces of spirits) on a social occasion is likely to experience a period of mild release of inhibitions which often passes as a pleasant state of stimulation. However, sedative/hypnotic drugs do not exert true stimulant effects: "The apparent stimulation results from the unrestrained activity of various parts of the brain that have been freed from inhibition as a result of the depression of inhibitory control mechanisms" (Ritchie, 1975). This effect is termed "disinhibition."

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[9] Duration of action delineates the length of time that a drug continues to exert its major effects.

[10] Doses which are ordinarily insufficient to produce sleep in a given nontolerant individual.

In recent years, there has been a dramatic decline in the prescribing of these drugs for daytime sedation. Although very regular use of sedative/hypnotics tends to produce tolerance rapidly to their unwanted low-dose side effects, tolerance to the desired psychological effects also rapidly develops. To compensate, higher daily doses may become necessary and can significantly increase the severity of side effects and the risk of dependence and abuse.

Generally, for sedation purposes the sedative/hypnotics have been replaced by the minor tranquillizers, most often the benzodiazepines. These compounds tend to produce fewer and milder side effects, are much less likely to produce serious physical dependence problems, and if taken in overdose quantities are less lethal by far than overdose of sedative/hypnotic drugs.

At one time, phenobarbital was the most commonly used drug for the management of certain types of epileptic seizures, such as grand mal and cortical focal seizures.[11] (Focal seizures, less general than the grand mal type, ordinarily affect only one side of the body.) However, its widespread prescribing for this purpose is not as great as in the past because of the introduction of new anticonvulsant drugs such as phenytoin (e.g., Dilantin). Phenytoin is more effective than phenobarbital in controlling grand mal seizures and does not pose the risk of dependence associated with barbiturates. Nonetheless, phenobarbital continues to be prescribed by many physicians, often in combination with phenytoin, because (1) the combination provides a greater overall anticonvulsant effect and (2) phenobarbital is the more effective in controlling focal seizures.

Effects of Hypnotic Doses (Moderate Doses)[12]

Unquestionably, the major clinical use of sedative/hypnotics is in the management of sleep disorders. Regardless of purpose of use, however, shortly after the administration of a sedative/hypnotic and before the onset of sleep, a number of side effects typically occur. The most important result from increased depression of the CNS and can include general impairment of fine and gross motor functions (e.g., speech may become slurred), increased difficulty in carrying out complex motor tasks, such as driving or using other machinery, perceptual impairment, and increased reflex reaction time. Some users also experience varying degrees of impairment of thought and memory as well as of other cognitive functions. A pleasant state of sedation occurs in many users. However, as with low doses, setting and expectations play a significant role in the emotional responses and behavior of any given user. While some experience euphoria, others experience decidedly dysphoric reactions such as feelings of hostility or depression. Because behavioral disinhibition increases with moderate doses of sedative/hypnotics, hostile feelings may be translated into action. Truculence,

[11] While most barbiturates have anticonvulsant properties, phenobarbital is the drug of choice because it has a lower dependence liability and a longer duration of action than other barbiturates.

[12] Doses which are ordinarily sufficient to produce sleep in nontolerant individuals. Of course, the size of dose necessary to produce this effect varies from one sedative/hypnotic to another and from one user to another. It should be kept in mind that even for some nontolerant individuals, quite large doses of alcohol (or other sedative/hypnotics) may be necessary to produce sleep—i.e., doses sufficient to produce a state of inebriation.

belligerence, and assaultive behavior, for example, are a common result of alcohol consumption in our society.

Moderate doses of sedative/hypnotics taken by healthy adults do not ordinarily exert harmful respiratory or cardiovascular effects. However, mild respiratory depression and a small drop in blood pressure often occur.

The "hangover" effect (fatigue, headache, nausea) is not exclusive to the use of alcohol, but can occur with hypnotic doses of other sedative/hypnotic drugs as well.

Normal Sleep

Because chronic sleep disorders are so common in our society and often result in harmful consequences, extensive research efforts have been directed towards combating them. However, our knowledge in this area remains meager. In fact, even our understanding of normal sleep and of the many phenomena occurring during sleep is quite limited. In order to understand better the effects of barbiturates and other sedative/hypnotics on sleep, a brief discussion of the highlights of what is known about the normal drug-free sleep process is presented.

It is generally agreed that sleep is biologically essential, and that under most conditions a sleep-deprived person experiences adverse and sometimes drastic psychological consequences. Furthermore, interference with certain periods of sleep (by selectively wakening the sleeper during these periods) can produce similar harmful consequences.

Using the electroencephalogram (EEG), which measures electrical activity in various areas of the brain, and also using measures of sleep activity, researchers have found that there are two distinct phases which cyclically recur during normal sleep, often referred to as REM (rapid eye movement) and nonREM sleep. The nonREM phase, which normally accounts for 75% of total sleep time, comprises four stages, and the depth of sleep (i.e., the difficulty in wakening the sleeper) increases as the sleeper progresses from stage one to stage four. During each stage the brain produces different amounts of electrical voltage and distinct types and patterns of EEG waves.[13] The significance of these different stages is not yet understood; however, it has been demonstrated that depriving a person of a given stage of sleep prevents progression to later stages.

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[13] For example, EEG recordings taken during the stages of deep sleep (stages three and four) appear as high-voltage, synchronized slow waves; the combination of these two stages is known as "slow-wave sleep."

Relatively little dreaming occurs during the nonREM sleep phase, although night terrors and somnambulism, when they occur, do so during stage four sleep. Throughout nonREM sleep, there are frequent slow, rolling eye movements, and muscle tone tends to be only slightly below that of the relaxed awakened state.

About 90 minutes after the onset of sleep there is an abrupt and rapid transition from the fourth stage of nonREM sleep to REM sleep. During REM sleep, (1) the eyes constantly oscillate beneath the eyelids, (2) there is complete relaxation of the skeletal muscles, and (3) persons wakened at this time will usually report that they were dreaming.[14] One REM sleep episode lasts for 20–30 minutes (accounting for approximately 20%–25% of total sleep time). After the completion of REM sleep, the entire cycle is repeated three to four more times throughout an uninterrupted eight-hour period of sleep.

It has been clearly demonstrated that the body requires REM sleep. In sleep studies it has been shown that if REM sleep is systematically disrupted by repeated wakening of the subject during the REM phases, even though the other phases during the sleep are allowed to continue without interruption, the body will try to increase the frequency of REM episodes in order to make up the deficit. Deprivation of REM sleep by such selective wakening can result in agitation, depression, inability to concentrate, and erratic and in some cases psychotic behavior. These effects rapidly disappear when REM sleep is again permitted.

One hypothesis to acount for REM sleep is that during this phase the brain is consolidating and discarding, where appropriate, the massive amount of information taken in during the waking hours of the day; as such, it is a necessary process. A neo-Freudian theory, on the other hand, suggests that during REM sleep the brain engages in those behaviors which it cannot allow in the awakened state because of inhibitory controls and that such release during sleep is desirable in contributing to stable behavior during waking hours.

[14] Anxiety dreams, nightmares, and other vivid dreams are more likely to occur during REM rather than nonREM sleep.

Sleep Disorders and the Use of Sedative/Hypnotics

Sleep disorders are symptoms usually of situational stress, psychological problems, or medical illness. The decision whether or not to prescribe a drug to combat a sleeping problem, and which drug and for how long, depends not only on the symptom but also on the cause. For example, if the onset of sleep is interfered with by a painful medical condition, an analgesic rather than a sedative/hypnotic is likely to produce the desired result. In the case of emotional depression, sleep dysfunctions often improve with the use of antidepressants; with anxiety states that produce sleeping problems, minor tranquillizers are the preferred drug intervention. In all such cases not only are these specific drugs in the long run more appropriate than sedative/hypnotics, but they are also far safer.

For insomnia and other sleep disorders created by temporary and emotionally stressful conditions, sedative/hypnotics (sleeping pills) are the most common and often the most relevant form of short-term intervention. Likewise, for occasional sleeping problems, sedative/hypnotics are appropriate and ordinarily not harmful. However, long-term regular use of sedative/hypnotics to combat such common problems as chronic insomnia or frequent nighttime awakening is usually ineffective and can have deleterious effects on the user for the following reasons:

1. For those sleeping difficulties which are symptomatic of psychological problems (the most common cause of sleep dysfunction), the use of sleeping pills merely masks the underlying cause. The original sleep disturbance will very likely recur after the termination of sedative/hypnotic therapy provided no other therapeutic intervention is concurrently undertaken during the course of treatment. In the long run, psychotherapy and professionally supervised relaxation training are sensible approaches to the recovery of healthy sleeping patterns; the former addresses the underlying problem, while the latter deconditions body tension which in insomniacs is often associated with going to bed.

2. Tolerance to the sleep-inducing properties of almost all commonly prescribed sedative/hypnotics can develop very rapidly with everyday use. In fact, these drugs retain little sleep-inducing effectiveness after one to two weeks of nightly administration. (An important exception, however, is flurazepam; it has been demonstrated under sleep research conditions to retain much of its potency with repeated administrations for at

least four weeks.) Because insomnia can be so distressing, many patients using sedative/hypnotics compensate for growing tolerance to the drugs by increasing their bedtime dose. The larger dose, however, is only temporarily effective, and soon thereafter the patient may feel compelled to resort to even higher doses—a state of affairs which can lead to serious dependence problems and to other potentially hazardous consequences.

3. While sedative/hypnotics can initially induce sleep and increase the number of hours of continuous sleep, they can also adversely affect important aspects of normal sleep. At typical doses, most sedative/hypnotics suppress REM sleep, with the result that patients often complain of a poor quality of sleep; upon awakening, they do not feel well rested.[15] The problem seems to be heightened when the patient is taking a sedative/hypnotic ordinarily characterized as longer-acting rather than (molecularly) equivalent doses of one of the so-called shorter-acting type. Although drug-induced suppression of REM sleep (similar to experimental REM sleep deprivation) is not normally as serious as it was once thought to be, nonetheless it can produce a spectrum of harmful psychological consequences, ranging from mild daytime restlessness to quite severe psychotic reactions. Furthermore, cessation of drug use after several consecutive nights can result in a temporary increase in the frequency of nightmares.

During an extended period of nightly sedative/hypnotic administration, tolerance can develop to the suppression of REM sleep, and therefore the amount of REM sleep may return to close to normal. However, even a person tolerant to a sedative/hypnotic drug is likely to experience a "rebound" increase in REM sleep to well above normal when its use is abruptly discontinued. Although this temporary state constitutes a simple withdrawal reaction from the drug, the person experiencing it may interpret it as the return of the original sleep disturbance. It is important that physicians prescribing a sedative/hypnotic inform the patient of the possibility that this type of problem will exist for a few nights after the drug has been abruptly discontinued. Otherwise the patient may revert to regular use of the drug and be caught in a cycle of sleep dysfunction, sedative/hypnotic use, cessation of sedative/hypnotic use, back to sleep dysfunction.

[15] The effect tends to be minimal with typical hypnotic doses of chloral hydrate and with low hypnotic doses of flurazepam and methaqualone.

Those recurring periods of deepest sleep (stage four) are also significantly suppressed by many sedative/hypnotics—in this case, including flurazepam. In some instances, the "rebound" effect of suppressed, and therefore shortened, stage four sleep is day terrors and even suicidal thoughts.

Effects of Anesthetic Doses (Higher Doses)[16]

General anesthesia is a drug-induced state of unconsciousness so profound that no external stimuli can rouse the patient to consciousness, and therefore even the greatest levels of pain (such as during surgery) are not experienced. This degree of CNS depression can be induced by many substances, including all of the sedative/hypotics; however, very few drugs in this class are clinically used as anesthetics. At doses high enough to produce anesthesia, most sedative/hypnotics would also produce dangerous and uncontrollable side effects such as severe respiratory depression and to a lesser extent cardiovascular depression; death may result from respiratory arrest.

A few ultrashort-acting barbiturates, such as thiopental, can be administered intravenously in doses sufficient to induce general anesthesia (i.e,, 100–200 mg) without normally producing harmful side effects. Unconsciousness follows as rapidly as 10–20 seconds after the initial dose. The ultrashort-acting barbiturates can be employed either alone in brief surgical procedures (usually those taking less than 15 minutes) or, in more lengthy procedures, to initiate anesthesia before the anesthetist switches to a maintenance drug, such as a gaseous anesthetic.

ABUSE OF SEDATIVE/HYPNOTICS

While alcohol belongs to the sedative/hypnotic class of substances, the scale of its abuse elevates it to a class by itself. In the discussion below, therefore, abuse of alcohol will be treated separately in the first section, followed by a section dealing with other sedative/hypnotics.

ABUSE OF ALCOHOL

Alcohol is unique among the psychoactive drugs which pose serious health, social, and legal problems in our society—unique because it can be legally obtained by adults without a physician's prescription. Moreover, its easy availability, its high degree of social acceptability, and the widespread desirability of its psychoactive effects are factors which in combination all too easily allow abuse, with harmful consequences for both the abuser and others. In fact, the incidence of socially deviant behavior resulting from abusive drinking is undoubtedly far greater than that caused by all other drugs of abuse combined.

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[16] Doses which are ordinarily sufficient to produce anesthesia in nontolerant individuals.

Violent Behavior

Alcohol depresses the inhibitory/emotional control centres of the brain. Although there are substantial individual variations in type and intensity of response, generally greater emotional disinhibition is likely to be observed as the amount of alcohol consumed increases per unit time. In most instances, external controls, as well as a lifetime of training, are ordinarily sufficient to dissuade most people from engaging in outwardly directed violent behavior. However, many studies have found that in the majority of violent crimes, the attacker, the victim, or both have consumed alcohol. Aggressors and victims also are often known to each other or are related. In fact, clinicians working with the families of male alcoholics find that the large majority of the subjects' wives have been the victims of physical abuse by the husband at least once and frequently more often. The same is true for the children of alcoholics, irrespective of the sex of the drinking parent.

While a past history of alcohol-related violent behavior is the best index of future violent behavior, it is very rare to find an individual who behaves violently on all drinking occasions. Rather, given the sheer number of drinking episodes which have occurred without violent incident, in the lifetime of the sometimes violent drinker the violence is a relatively infrequent event. Also, given the enormous number of drinkers in our society, only a very small fraction behave violently at any time in their lives, even after heavy alcohol consumption.

Alcohol-related violence is a complex interpersonal phenomenon. For the aggressor or aggressors, high-dose alcohol consumption can impair judgment, reduce the frustration tolerance threshold and the effectiveness of personal controls, increase the likelihood of risk-taking behavior, and often produce inflated confidence. These effects tend to create some of the conditions conducive to the destructive interpersonal behavior that we term violence. So-called "senseless" violence without any apparent motive and without serious psychological disturbance is relatively infrequent with the use of alcohol.[17]

The behavior of the victim in such exchanges need not be hostile in order to provoke violence, although mutual hostility is not unusual when both aggressor and victim have been drinking. Avoidance behavior may actually provoke hostility even when the victim may thereby be attempting to reduce provocation. Avoidance may be interpreted by the drinking aggressor (often correctly) as fearfulness; and fearfulness has been demonstrated to increase the probability of aggressive and attack behavior in humans and many animal species even when alcohol is in no way involved.

Social class and culture have been demonstrated to be factors in alcohol-involved violence. Violent behavior is significantly more likely to occur among drinkers of lower social status. It is generally acknowledged that modes of aggression in any given social class are related to the range of acceptable behaviors within that social class and to language facility. In higher-status groups, physical violence is highly unacceptable under all but extraordinary conditions, whereas a certain degree of verbal aggression is tolerated. Lower-status groups tend to permit somewhat greater latitude with regard to physical aggression, partly because their members usually do not possess the verbal facility to manifest aggression in the sophisticated and frequently disguised manners of higher-status aggressors. The former, therefore, are more likely to resort to physical expressions of hostility both when drinking and when sober.

Some cultural groups, such as Jews, will not countenance either physical or verbal alcohol-involved aggression within their numbers.[18] Southern Europeans condone daily consumption of fairly large quantities of alcoholic beverages (mainly wine), but drunkenness and alcohol-involved abusive behavior are not permitted. By contrast, native Indians throughout North America and blacks and Spanish-speaking subcultural groups in the impoverished core areas of large

[17] By contrast, for example, in the case of violence perpetrated by someone in a state of amphetamine-induced psychosis, the actions are based on an internal delusional system which results in a highly impaired ability to interpret reality correctly.

[18] The role of alcohol in the traditional Jewish culture is mainly ritualistic, and therefore to abuse alcohol would be highly improper. Similarly, in traditional Japanese culture, alcohol has primarily a ceremonial function, and alcohol-related aggression would be a serious social offense.

American cities have high rates of alcohol-involved violent behavior. However, this behavior is related less to ethnic characteristics than to the norms and subcultures created by poverty, frustration, and the relative acceptance of alcohol and other drug abuse.

Self-Destructive Behavior

Many people resort to alcohol in order to relieve emotional depression. Unfortunately, however, its disinhibiting effects can exacerbate their depression. Moreover, it increases the possibility of impulsive behavior and in large doses can severely impair judgment. This combination of effects has often resulted in suicidal behavior in clinically depressed people. One recent review of the literature reported agreement among investigators that around the world alcohol abuse is frequently associated with high rates of suicide (Motto, 1980).

While the incidence of alcohol-involved suicide attempts is not known, autopsy data have revealed the presence of alcohol in the blood or stomach of one in four successful suicides. A large-sample American study found the presence of alcohol in the blood of more than one-third of those whose death resulted from self-inflicted gun wounds.

Alcoholics have a particularly high rate of suicide. World Health Organization (1968) data indicate that almost 20% of suicides worldwide have been identified as alcoholic. Although statistics for Canada are not available, alcoholics represent the largest distinguishable group among suicides in the United States and account for roughly 30%.

Drug overdose is the most common form of suicide attempt. Alcohol taken alone can produce lethal results if very large quantities are rapidly consumed (e.g., 60–80 cl, or 20–30 oz, of 100 proof whiskey within an hour or less). However, most successful suicides, as well as many accidental deaths, involving alcohol overdose also involve concurrent overdose of other drugs, usually other sedative/hypnotics and to a lesser extent the benzodiazepine tranquillizers. While overdose quantities of benzodiazepines are rarely fatal when consumed by themselves, the risk of death is enhanced when they are taken in combination with alcohol, for large amounts of benzodiazepines can dangerously increase the respiratory-depressant effects of large amounts of alcohol. When high doses of alcohol are combined with such potent sedative/hypnotic drugs as barbiturates, the lethal risk is much greater, as both agents can profoundly depress the respiratory control centres in the brain.

Drinking and Driving

Driving an automobile is a complicated task; the addition of alcohol makes it even more complex. Driving involves three things: skill (the ability to perform), processing (making judgments while doing a number of things), and attitude. It should be noted in the following discussion that the same factors apply to flying airplanes, driving boats and snowmobiles, or handling any motorized vehicle or complex machinery.

As far as the effect of alcohol on driving skills is concerned, it has been found that a driver's reaction time is not remarkably affected by alcohol. There is no simple relationship between the blood level and impairment. At low blood levels there can be a slight improvement of performance, possibly due to relaxation. This is followed at higher levels by a more significant deterioration. In general we can say that well-learned tasks are less affected by alcohol than newly learned tasks and that tasks akin to natural movement are also less affected. However, driving is not just a composite of individual tasks such as stopping/starting. Its related tasks involve the brain's ability to process information and to make judgments; and alcohol has a much greater and more deleterious effect on processing information than on physical skills.

Driving is a "divided attention task." That is, it involves several simultaneous tasks. Impaired drivers whose physical driving skills may not be adversely affected by relatively low blood alcohol levels may nevertheless become involved in accidents because they cannot quickly enough integrate the many pieces of information that must suddenly be considered in an emergency or in a suddenly complicated driving situation.

Possibly the most dangerous effect alcohol has on driving, however, is on the driver's attitude. It has been found to increase one's willingness to engage in risk-taking behavior. Obviously, increased risk-taking increases the probability of accidents. This alteration in the risk-taking threshold is not related to ability to perform the necessary maneuvers or to process information.

An oft-cited example of the increased risk-taking threshold is a British experiment by Cohen et al. in 1958. Bus drivers, after drinking, were asked to drive through a gap between a pair of light standards. Some drivers received no alcohol, others received 2 oz (5.9 cl) of whiskey, and a third group received 6 oz (17.8 cl) of whiskey. Drivers were asked to indicate the narrowest gap through which they thought they could always drive their buses, and the width of gap through which they were willing to try. Finally, drivers had to attempt to actually drive through the gap.

Both the control group and the group which took 2 oz (5.9 cl) of whiskey thought they could always drive their buses through a gap of 8 ft. 1½ in. (This figure and the following are averages.) The control group was able to get through a gap of 8 ft. 6½ in. and the other group through a gap of 8 ft. 7 in. After they had drunk 6 oz (17.8 cl) of whiskey the final group thought they could always get through a gap of only 7 ft. 10½ in., but actually got through a gap of 8 ft. 7½ in. It is interesting to note in addition that three of the drivers who had only had the 2 oz (5.9 cl) of whiskey were willing to attempt to drive through a gap that was actually 14 in. narrower than their buses.

The ability to drive may also be impaired by other drugs taken for therapeutic reasons which also produce CNS-depressant effects. Well-known examples would be tranquillizers and barbiturates. When these are taken in combination with alcohol, significantly greater impairment is probable. However, certain other drugs are less commonly known to adversely affect driving performance—antihistamines, for example, the side effects of which may include drowsiness and sedation. Similarly, when antihistamines are taken in conjunction with alcohol, driving ability is likely to be even more adversely affected. In fact, if a driver has consumed any drug which may produce such side effects, any quantity of alcohol cannot be safely consumed.

Breathalyzer Measurement of Blood Alcohol Levels

Most modern societies have devised laws which permit the police in certain circumstances to enforce measurement of blood alcohol levels of those whom they suspect to be impaired at the wheel of a car. These laws are in response to the large number of deaths and disabling accidents which are associated with the consumption of alcohol. Though there are a variety of ways of measuring blood alcohol levels, the most common method currently in use is the Breathalyzer, a machine which allows rapid measurement of blood alcohol levels by analysis of breath samples. The technique works because alcohol is volatile at body temperature.

The breath allows accurate determination of blood alcohol levels for the following reason. Ethyl (beverage) alcohol after being absorbed into the bloodstream is rapidly delivered to the lungs, where it equilibrates with air in the little sacs known as alveoli. (That is to say, the amount of alcohol in the air in the lungs is directly proportional to the concentration of alcohol in the blood passing through the lungs.) Because of the equilibrium between lung air and lung blood, a test of lung air is an accurate reflection of the lung blood alcohol level. In human beings, at equilibrium, 2,100 volumes of air contain as much alcohol as one volume of blood. This ratio is constant in all humans and has been confirmed and officially certified as a standard measurement by the United States National Safety Council's Committee on Alcohol and Drugs. What the Breathalyzer does is measure the alcohol concentration in the lung air with great accuracy.

There are three steps in using the Breathalyzer. First, a deep lung breath sample is collected by having the subject blow into a piston constructed to retain the air last expelled from the lungs. The apparatus (piston) is then heated so that water vapor in the breath does not condense. (If the water were allowed to condense, the alcohol would dissolve in it, and the analysis of the breath would give much lower alcohol value than was really representative.) In the second step, the air is bubbled into a mixture of potassium dichromate and sulfuric acid plus a catalyst. This solution converts the alcohol into acetic acid and some of the potassium dichromate into chromic sulfate. The final step consists of measuring the concentration of the converted products. The potassium dichromate is yellow in solution, and the chromic sulfate is green. The amount of color conversion is directly related to the amount of alcohol destroyed. The whole procedure, then, is a matter of measuring the decrease in concentration of the yellow color. The less yellow the solution, the more alcohol existed in the original breath sample. The machine is designed so that this decrease can be read directly as blood level in a matter of minutes without calculation. This final conversion step is independent of outside factors and is not influenced by significant concentration differences in the solution components because only a change in color is measured. The most important variable is the dimension of the vial of solution used. The dimension of each is checked with a template provided with the machine.

Being able to measure blood alcohol in this way is important pharmacologically. Alcohol levels are related to lung blood which, after a short trip through the heart, goes directly to the brain. Thus lung blood alcohol levels correspond very closely to levels in the brain, and it is the brain level of alcohol which causes impairment.

The Breathalyzer is particularly valuable from a legal standpoint because it delivers the sample for analysis directly into the machine. There is no question of the sample being lost or mislabeled. However, if the subject is unable to be brought to a machine, a breath sample can be collected in a plastic bag and stored for 48 hours; it is then analyzed in the normal manner and will yield the same results as if it were tested at the same time as collected. Users of the machine have a checklist of steps which, if followed closely, result in very high replicability and accuracy of blood alcohol level readings.

If alcoholic beverages or oral preparations containing alcohol (e.g., some mouthwashes and cough medicines) are consumed just before a Breathalyzer measurement, there will be a falsely high reading; however, this misleading effect will disappear in less than 15 minutes. It is standard procedure, therefore, to observe subjects to see that they take nothing containing alcohol by mouth for at least that period. The same delay is also necessary following vomiting.

Other factors make a slight but not significant difference to the blood alcohol measurement. Foods which have a strong odor, such as garlic and onions, have no appreciable effect on the determination. The acetone on the breath of diabetics is not a significant factor in the apparent blood levels; nor are the increased amounts of acetaldehyde excreted by the lungs of people using Antabuse.

Nonbeverage alcohols (e.g., isopropyl alcohol) and paraldehyde will react to the Breathalyzer in the same way as ethyl alcohol. However, the presence of these materials can be detected either by odor or by other means and can easily be differentiated from ethyl alcohol by their different rates of reaction. For ethyl alcohol, the measurement will be the same at 90 seconds as at 120 seconds. For these other substances, the 120-second reading will be appreciably higher.

Blood alcohol values can be expressed in a variety of ways, but the level is usually given as a percentage indicating alcohol weight in grams per 100 milliliters of blood volume. By this system the legally prohibited blood level in Canada, for example, would be more than 0.08 g (*absolute* ethyl alcohol)/100 ml. In Continental Europe, however, the level is given in grams per liter; thus the same impairing value would be expressed as more than 0.08 g/l. In a third system the level is given in milligrams per 100 milliliters, and the same value would be expressed as 80 mg/100 ml.

Though there are varying legal blood level values in different jurisdictions (0.05%, 0.08%, 0.10%, 0.15%), with a general tendency to enforce the lower levels, the purpose in all cases is the same. Blood levels serve as a legal benchmark and constitute reliable evidence for prosecution of drinking drivers.

While it is generally true that people with higher than legal blood alcohol levels are impaired, it has been argued that a person may exceed these blood levels and drive as well as someone else who has no blood alcohol level. However, the traffic system operates on a societal level of competence. The already difficult traffic situation would become impossible if people drove at their minimum level of competence. Like legal speed limits, legal blood alcohol levels are not foolproof predictors of whether any single individual is driving better or worse than the mean response of the population of all drivers. What these levels really say is that people who exceed them are at greater than acceptable risk with respect to impairment of their own driving skills.

For a simple overview of blood levels, we can say that below a blood level of 0.05% most but not all drivers are reasonably safe from alcohol-induced impairment. (This assumes that a driver has not consumed any other drugs which could add to impairment.)

As the level approaches 0.08%, the drinker moves progressively into the area of impairment. Blood levels of 0.15% to 0.25% are clearly an area of frank intoxication. At blood levels approaching 0.40% and higher, the person is "dead drunk," and levels not much higher than this (0.50% and higher) is an area of lethality.

The question of concern to many people is how many drinks it takes to produce the above effects. To answer this question, it is necessary to review some of the basic pharmacological considerations surrounding the ingestion of alcohol. Alcohol is consumed in a diverse number of beverages. All alcoholic beverages are essentially alcohol–water solutions containing very small amounts of miscellaneous substances. The alcohol in the beverage is absorbed partly through the stomach but predominantly through the intestines. The rate of absorption is affected by the type of alcoholic beverage ingested, the stomach contents, and whether or not the drinker's stomach is damaged. Very highly concentrated alcoholic beverages (e.g., brandy) can cause pylorospasm, an acute abnormal muscular contraction of the sphincter between the stomach and the intestine, which prevents the stomach from emptying and thereby retards absorption of the alcohol. Similarly, if the stomach contains significant amounts of food, stomach emptying may also be retarded, and the absorption of the alcohol thus slowed. If the drinker has undergone a whole or partial gastrectomy (removal of stomach), however, alcohol will pass very rapidly into the intestines and the rise in blood alcohol level will then be very dramatic. The drinker may become both legally and behaviorally impaired at levels of consumption which would not cause a normal person any difficulty. It should be emphasized that alcohol requires no digestion. It is absorbed unaltered directly into the bloodstream.

Alcohol is metabolized at a constant rate, but the rate may differ somewhat from person to person. That is, everyone metabolizes a certain fixed amount of alcohol per hour, independent of the blood level at the time the metabolism is taking place. The individual's maximum rate of metabolism is reached at very low blood levels. For all practical purposes, from the first drink ingested the liver is metabolizing at a constant and maximal rate.

In the average man weighing 70 kg (154 lb) the approximate rate of metabolism is two-thirds of one standard drink per hour. A standard drink is here defined as 1.5 oz (4.4 cl) of 80 proof distilled spirits, 3 oz (8.9 cl) of fortified wine such as sherry, 5 oz (14.9 cl) of table wine, or 12 oz (35.5 cl) of Canadian beer. The average man could thus drink a standard drink every hour without accumulating significant blood alcohol levels. A smaller person will be able to metabolize proportionately less alcohol per hour, while a larger person of normal weight for height will metabolize proportionately more.

Thus, a small person consuming the same amount of alcohol as a large person will have a higher blood alcohol level than the large person. In effect, the small person gets a higher blood alcohol concentration than the large person from an equal amount of alcohol because there is less body water in the small person to dilute the same amount of alcohol. However, the blood alcohol concentration in the large person will decrease at the same rate as for the small person. Small people are therefore at a disadvantage if they drink the same amount of alcohol because it will take much longer for their blood alcohol level to reach zero.

CHRONIC ABUSE OF ALCOHOL

Definitions of Alcoholism

There are several commonly accepted definitions of alcoholism in current use. The World Health Organization (WHO) defines alcoholism as an impairment resulting from alcohol abuse which can be manifested in "a noticeable mental disturbance or an interference with . . . bodily and mental health, interpersonal relations, and . . . smooth social and economic functioning." The Addiction Research Foundation of Ontario (1976) has defined alcoholism in terms of the quantity of alcohol consumed on a regular basis; an average consumption of at least 15 cl of absolute alcohol per day for males, and two-thirds that amount for females, is said to constitute alcoholism.[19]

Jellinek, a pioneer in the field of alcoholism, essentially agreed with the WHO definition, but also proposed that alcoholism is a distinct disease. He contended that a true state of physical dependence occurs in the large majority of alcoholics and that most alcoholics cannot control their intake. While many specialists now believe that alcoholism is primarily a psychological rather than a medical disorder, there is no question that Jellinek's illness model of alcoholism was largely responsible for effectively challenging the widely held belief that alcoholism is a state of moral degeneracy.

Some researchers have completely dispensed with the term alcoholism in favor of a numerical scoring system which looks at a variety of problems related to alcohol abuse (e.g., legal problems, work problems). Their approach provides an alcohol-related "problem score" and permits relative comparisons among individuals or groups of individuals. The major advantage of this orientation is its avoidance of one of the more controversial issues: the arbitrary labeling of alcohol users as either "alcoholic" or "not alcoholic" based on a formal inflexible definition.

Whichever definition one uses to arrive at an understanding of chronic alcohol use, there are a number of factors which must be examined to supplement any definition.

Drinking Patterns and Types of Alcoholism

Drinking patterns and therefore associated types of alcoholism vary from one culture to another. A well-known European style of drinking involves the everyday consumption of wine. If large enough amounts are consumed on each occasion, this style of drinking can produce a form of alcoholism characterized less by drunkenness than by a high rate of alcohol-related diseases and deaths.

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[19] Females, to the extent that they have a lower lean body mass and therefore less body water, will manifest behavioral and physiological impairment at lower consumption levels.

A contrasting drinking style common in North America is known as weekend drinking. A significant percentage of North Americans drink irregularly and modestly throughout the week but indulge in heavier drinking, mostly of beer and distilled spirits, on the weekends. If abusive quantities are consumed continuously throughout the weekend, the practice constitutes one manifestation of a form of alcoholism known as binge drinking. Other binge drinkers may abstain for extended periods of time and then engage in extremely abusive drinking for several days and in some cases for much longer. All forms of binge drinking are likely to be severely harmful to the drinker and may place in jeopardy both his or her own family and social circle and often other innocent members of society.

In North America there are also other widely recognized stereotypes of alcoholism, two of the most visible being skid row drinkers and the more socially integrated drinkers who consume large quantities of alcohol every day or on most days. Drinkers in the latter group, after their first drink, usually lose control over their alcohol consumption and tend to drink until they are intoxicated or fall asleep. This is the most common form of alcoholism encountered in North America. It has been estimated that skid row alcoholics represent only 3% of the alcoholic population.

All of the above drinking behaviors can be legitimately described as alcoholic; however, there are a large number of alcoholic states and conditions that lie somewhere between daily abuse of alcohol and intensive bouts of binge drinking.

Causes of Alcoholism

Our understanding of alcoholism is still in the theoretical and speculative stage, and there are several widely held theories or models that attempt to explain its roots or causes.

Some genetic/biological theories propose that alcoholism results from inherited metabolic abnormalities such as an enzyme deficiency or an endocrine imbalance. Such theories stem from the fact that there is a much higher rate of alcoholism among the offspring of alcoholics than of nonalcoholics. However, no specific genetic abnormality has yet been found generally to occur in alcoholics; furthermore, some critics have suggested that the higher rate of alcoholism among children of alcoholics may be due to behavioral coping styles learned at an early age.

Many investigators in the field of personality theory have stressed a psychodynamic cause for alcoholism. Considerable attention has been directed toward the search for common personality characteristics and abnormalities underlying alcoholism—that is, a search for the alcoholic personality. However, researchers have concluded that no currently available scale is able to discriminate accurately between alcoholics and nonalcoholics. Virtually every widely used objective measure of personality has been tried with generally disappointing results.

Other investigators have proposed a behavioral model of alcoholism. In this scheme, alcohol is viewed as a drug which can rapidly reduce tension and anxiety, replacing unpleasant feelings with a state of relaxation, disinhibition, and pleasurable intoxication. For the drinker, the too frequent pairing of alcohol consumption with tension reduction and the concomitant pleasurable effects have several negative implications. The drinker:

- resorts to alcohol in an ever-increasing variety of stressful situations, even in those in which the stress is relatively mild;
- engages in an increasing frequency of drinking under nonstressful conditions in order to achieve desired alcoholic effects;
- may ultimately consume alcohol in part to relieve the stress produced by its absence in the body.

Finally, many observers believe that sociocultural factors play an important role as determinants of alcoholism. They correctly note that the rate of alcoholism is the highest in those cultures that have a permissive attitude toward regular alcohol consumption and in those cultures in which alcohol is the most freely available.

It should be stressed that none of the above positions is exclusive to the point where it is totally incompatible with any of the others. The causes of alcoholism appear to be complex, and it is quite possible that a number of factors contribute to the development of this pervasive problem.

Alcohol Abuse and Medical Problems

Many of the adverse organic effects of chronic alcohol abuse are insidious and can adversely affect most organ systems of the body.

However, its most demonstrable effects are exerted on the organs of the gastrointestinal tract, the cardiovascular system, and the nervous system. Harmful medical consequences can be divided into two major groups:

- those directly related to chronic heavy alcohol consumption, such as cirrhosis of the liver; and
- those secondary to chronic heavy consumption, such as diseases resulting from the accompanying nutritional deficiencies common to chronic alcoholism.

It has been shown that after several years of average daily consumption of 5.0–7.5 cl of absolute alcohol (i.e., 4.2–6.3 oz of distilled spirits) drinkers significantly increase their risk of cirrhosis and of certain types of cancer (e.g., of the esophagus) over drinkers with lower average daily consumption rates. The risks are still greater with higher consumption rates.

Brain deficits related to chronic alcoholism gradually develop over several years. Among the first to develop are blackouts, a little-understood phenomenon which is actually a form of antegrade amnesia resulting after a given blood alcohol level has been attained. The amount necessary to trigger blackouts can differ significantly from one drinker to another. Blackouts appear to be unrelated to the individual's memory capacity while sober, but rather are associated with a cluster of factors including (1) frequent drinking until intoxicated or falling asleep; (2) increasing tolerance to alcohol; (3) loss of control over drinking; and (4) history of head injuries. Later symptoms which can appear in both sober and intoxicated states include deterioration of emotional restraint, confusion, impairment of articulation, increasing inability to reason abstractly, and impairment of ability to coordinate perceptual/motor functions. These, when combined with progressive degeneration of the cerebellum (that area of the brain controlling certain motor functions themselves), can result in the alcoholic's appearing to be drunk even when sober.

Numerous other central and peripheral nervous disorders of uncertain pathogenesis have been reported to occur in certain chronic alcoholics. Among the most severe is the clinical picture of often irreversible polyneuropathy and organic psychosis, the Wernicke-Korsakoff syndrome, which appears to be related to both decades of nutritional deficiency and chronic intoxication. It is typically so incapacitating that permanent institutional care is often necessary.

As well as cirrhosis of the liver and cancer of the esophagus, other diseases of the gastrointestinal system which have a substantially higher incidence among chronic alcoholics than among the normal population are: acute gastritis during drinking episodes, peptic (but not duodenal) ulceration, chronic pancreatitis, fatty liver, and alcoholic hepatitis.

Incidence of cardiovascular and respiratory diseases among alcoholics is also greater than among the normal population. However, given that alcoholics also tend to be heavy smokers, the degree of direct contribution of alcohol to most of these diseases is uncertain.

Alcoholism and the Family

There is increasing interest in the effects of alcoholism on the spouse and children of the alcoholic. Particular emphasis has been placed upon whether or not unique behavior patterns or certain psychological disorders are more likely to develop in alcoholic as opposed to nonalcoholic families. The risk of emotional problems for the children of alcoholics is considerably greater than for children in the general population, although not greater than for the children of parents with other serious psychiatric disorders. One pioneering author, Margaret Cork, based on her own clinical impressions, reported that 92% of offspring she studied who had at least one alcoholic parent were assessed as being from "fairly" to "very seriously" emotionally damaged. Subsequent research has generally substantiated her findings.

No unique behavior patterns have yet been uncovered for the wives of male alcoholics, and even less is known about the husbands of female alcoholics. Their strategies or coping styles range from attack to withdrawal, depending on their own predispositions and the behavior of the drinking spouse. Nevertheless, clinical observations consistently find wives to be hostile, despairing, and resentful of their life situation. Suicidal gestures or attempts to leave the alcoholic spouse are not uncommon, and the majority appear to need professional counseling.

Youthful Alcohol Abuse

Large-scale surveys of high school students taken throughout the 1970s in Ontario and in the United States indicated a clear trend at all age levels towards both increased occasional use and increased regular use of alcohol. A particularly disturbing finding in a recent (1980) survey sponsored by the American National Institute on Drug Abuse was that, among a representative sample of almost 18,000 high school seniors, close to 6% had consumed alcohol almost every day during the past 30 days. Many experts would view such regular alcohol consumption as one indicator of problem drinking. The figure is remarkably close to that in the adult population. Additionally, such well-known American drug treatment facilities as Synanon and Phoenix House, which rarely saw teenage problem drinkers prior to the 1970s, reported that by the middle of the decade, at any given time, between 10% and 50% of their residents were both problem drinkers and under the age of 17. A 1979 survey of Ontario high school students in all grades revealed that almost 20% of all students reported being "drunk" at least once in the previous month.

Researchers have found that youthful problem drinkers are more likely to be products of an unhappy childhood and/or a broken marriage, to perform more poorly in school, to have more legal troubles (i.e., arrests and convictions), and generally to be more poorly adjusted than are nonproblem-drinking youths. As well, they are more likely to abuse other drugs, and they tend to be more emotionally disturbed than older alcoholics.

Methods of Treatment

Almost every available form of psychotherapy and psychopharmacological therapy has, at one time or another, been attempted with alcoholics: specialized inpatient and outpatient programs, the administration of certain protective drugs such as Antabuse (disulfiram—see article in section 3), used only in the treatment of alcoholism, psychoanalysis, gestalt therapy, insight-oriented therapy, hypnosis, LSD, and a variety of behavior modification approaches.

Success rates vary considerably, with the variation appearing to depend somewhat on the definition of successful treatment outcome. For example, those studies that define success in terms of total abstinence from alcohol have had substantially lower success rates than those which define success in terms of improved control over drinking. Another key factor is the demographic profile of the alcoholic client: those who have an intact marriage, a good work history, and a stable place of residence tend to be more successful than those who do not. Length of time in treatment rather than on the type of treatment employed per se also appears to be related to successful outcome. Indeed, some researchers question whether type of treatment employed matters at all. Certain large-sample studies have found the type of treatment employed by the therapist to be unrelated to treatment outcome. These findings, however, have not been universally accepted, and are currently the subject of intense debate.

The average treatment success rate tends to be between 30% and 40% when the minimum criterion—a clear improvement in control over frequency and amount of alcohol intake—is applied.

Controlled Drinking versus Abstinence

Over the past two decades, one of the most lively debates among alcoholism specialists concerns whether or not alcoholics can be taught to drink in a controlled manner—that is, can become social drinkers. Several researchers have reported that such a goal is appropriate and achievable, while many others (as well as Alcoholics Anonymous) do not agree. There are several studies supporting each point of view, and a recent and extensive review of the literature indicates that neither side has proven its case. However, it may be that both can be effective and that success depends on quite specific (but not yet sufficiently defined) patient characteristics; some patients may respond positively to the controlled drinking approach, while for others abstinence is the only reasonable recourse.

ABUSE OF OTHER SEDATIVE/HYPNOTICS

BARBITURATES

Generally, abusers of barbiturates (and similar sedative/hypnotics) belong to two major groups: (1) those whose abuse career results as an outgrowth of legitimate medical use; and (2) those who abuse barbiturates from the beginning for recreational (i.e., nonmedical) purposes.

Many of the former group are likely unaware of the dependence-producing properties of barbiturates and accidently become dependent on them. For this group, the principal motivation for increasing their dose to levels producing physical dependence is the desire to combat insomnia, although some users are reacting primarily to the pleasurably intoxicating side effects of these drugs.[20]

Those who fall within the second group are primarily street drug abusers. They often use barbiturates interchangeably with alcohol, as the pleasurable effects are very similar. Recent Ontario surveys suggest that barbiturates are easily available to high school students, particularly older youths, but use is generally occasional.

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[20] Physical dependence on barbiturates does not ordinarily occur when they are taken at doses within the therapeutic range, although many investigators consider REM "rebound" to be a form of mild withdrawal.

Street abusers of narcotic analgesics such as heroin and oxycodone and of stimulants such as the amphetamines are also frequent barbiturate consumers. Among heroin users who are no longer able to achieve a high (using the often very diluted preparations available on the street) it is not unusual to seek euphoria via intravenous injection of combined heroin and barbiturates—a practice which can prove fatal. Amphetamine abusers often take barbiturates to control the agitation which may result from several consecutive days of high-dose amphetamine use. The latter group also frequently employ barbiturates for their euphoriant properties.

In recent years, methaqualone has become a popular drug of abuse in its own right because of its potent intoxicating properties; to some extent, it has replaced barbiturates on the street as the preferred nonalcoholic sedative/hypnotic drug of abuse.

Lethality

By weight, barbiturates produce greater respiratory depression than absolute alcohol. In fact, barbiturates are among the most lethal of the widely abused drugs: deaths have been reported after consumption of only three times the therapeutic dose. When combined with other CNS-depressant drugs (which also depress respiration), the probability of lethal consequences is increased.

In an American survey (1973–76) of drug-related suicides reported by medical examiners, barbiturates were implicated in more than 50% of all cases. Several accidental deaths from overdose among barbiturate-dependent persons have also been reported. In cases of dependency, while tolerance to the desired effects continues to increase, only slight tolerance develops to the respiratory-depressant effect. Therefore, if users continue to increase their regular dose, they also continue to reduce the margin of safety that separates them from death due to respiratory arrest. Unlike with the narcotic analgesics, there are no known specific antidotes to barbiturate overdose, or, for that matter, to overdose of any of the sedative/hypnotic drugs.

INHALANTS

Because inhalants (solvents) are cheap and readily available and users can crudely monitor their own level of intoxication, these drugs have been abused by some young people. Surveys of solvent abuse among high school students consistently find an inverse relationship between age and number of users in the school population. The ratio comparing the youngest to the oldest student users often exceeds 4:1. It has also been reported that most young solvent users graduate to other drugs of abuse as they grow older, although a few continue to use solvents into adulthood. Nevertheless, there are a large number who only occasionally and experimentally come into contact with these substances, usually as a result of peer-group pressure.

Regular solvent abusers, when compared to nonusers or experimental users, are more likely to be the products of unstable and broken homes, to have at least one alcoholic parent, to perform less well in school, to have a substantially higher rate of truancy, and to have had a poorer personal adjustment prior to their drug abuse; moreover, their personal maladjustment suffers further as a result of chronic solvent abuse.

Other problems associated with solvent inhalation are detailed in the article on inhalants in section 3.

TOLERANCE AND DEPENDENCE

With regular use, tolerance develops to the pleasurable effects of sedative/hypnotics as rapidly as within a few weeks. Higher doses are then required to maintain, but not necessarily increase, the original level of pleasurable effects. In the case of occasional use, on the other hand, tolerance does not ordinarily develop. Thus, for example, the social drinker who consumes moderate amounts of alcohol on no more than a half-dozen occasions per month is unlikely to acquire appreciable tolerance to its effects. However, chronic heavy drinkers may achieve a degree of tolerance so great that very large quantities of alcohol (often in excess of 20 oz [59.2 cl] of spirits daily) no longer result in pleasurable intoxication.

Regular use of any sedative/hypnotic will also result in its decreasing ability to produce either sedation or sleep; and again, if the individual desires to maintain these effects, daily dose increases are necessary. Among the barbiturates and other sleeping pills, tolerance develops to the following sleep-related effects: sleep induction, sleep maintenance (i.e., amount of uninterrupted sleep time), and suppression of REM sleep. Furthermore, increased tolerance has been observed to develop to the impairment of motor coordination and reaction time. Tolerance to the barbiturates' anticonvulsant actions does not appear to occur; nor does appreciable tolerance develop to the respiratory-depressant effects of any of the sedative/hypnotics.

Among sedative/hypnotics a high degree of cross-tolerance appears to develop, and once tolerant to the effects of one, the user will also be tolerant to a dose equivalent in effectiveness of most others, including alcohol. Pretolerance sensitivity is usually restored after a few weeks of complete abstinence from all of these drugs.

Psychological dependence on any sedative/hypnotic may develop with chronic use, irrespective of daily dose. In such an instance, the drug acquires a central role in the person's life and there is a persistent craving for its effects. Psychological dependence is not necessarily manifested as a need for daily use. For example, a person may feel a strong need to consume alcohol in order to achieve a comfortable state of functioning at social events, and indeed may even decide not to attend an event at all if no alcohol is to be served. At other times the person may drink infrequently and without compulsion.

Chronic high-dose use of alcohol, barbiturates, and the newer sleeping pills can result in physical dependence;[21] within the therapeutic dose range, however, barbiturates and these newer drugs can be administered daily without producing physical dependence. At very high doses any of the above drugs, when chronically abused, can produce physical dependence so severe that if use is abruptly terminated, the ensuing withdrawal sickness may be life-threatening. The possibility of delirium and grand mal seizures is also common to all of the above. The specific withdrawal sickness related to each drug is detailed in the respective articles in sections 3 and 4.

A high degree of cross-dependence can occur among alcohol, barbiturates, and other sleeping pills (except flurazepam); in sufficient doses each may partially or fully suppress the symptoms of withdrawal sickness produced by abrupt abstinence from another, provided that it is administered before the onset of delirium. Evidence indicates that once delirium occurs, no known drug is effective in suppressing withdrawal. Phenobarbital is often employed in medical settings to assist physically dependent users in withdrawing from other sedative/

[21] In the case of flurazepam, physical dependence has yet to be demonstrated.

hypnotics, with the drug administered in progressively reduced daily doses over a period of several days or weeks.

II. MINOR TRANQUILLIZERS

See the articles on the benzodiazepine minor tranquillizers (e.g., Valium) and meprobamate (e.g., Miltown) in section 3.

The minor tranquillizers are the most widely prescribed psychotherapeutic agents in the world for the following reasons:

1. At low therapeutic doses, these drugs are effective in the management of a variety of common emotionally stressful conditions.
2. Their side effects tend to be few and mild.
3. Their physical-dependence-producing propensities tend to be substantially lower than those of such drugs as the barbiturates.
4. They possess a wide margin of safety.
5. They have been widely promoted by the use of highly effective marketing strategies (which have recently become the subject of both governmental and media criticism).

Because these drugs have proven to be so effective in combating anxiety, they are also called antianxiety agents or anxiolytics.

HISTORY

In the past, those suffering from anxiety and tension states were treated with such CNS-depressant drugs as opium, alcohol, and other early sedative/hypnotics (e.g., paraldehyde and bromides), and more recently with barbiturates. None of these substances was satisfactory, as each produces a number of unwanted side effects as well as presenting significant tolerance and dependence problems.

Meprobamate, the first minor tranquillizer, was introduced in the mid-1950s as a muscle relaxant; however, it was discovered also to effectively relieve anxiety at low therapeutic doses without producing the level of sedation and drowsiness associated with most sedative/hypnotics. For this reason, meprobamate was widely endorsed and rapidly became the drug of choice in the treatment of many nonpsychotic psychiatric conditions. By the late 1950s, literally millions of prescriptions for meprobamate were written each year. Nonetheless, optimism about the benign nature of meprobamate was clearly premature. For several reasons to be discussed below (including the introduction of the benzodiazepines), it is now much less frequently prescribed.

The first compound belonging to the benzodiazepine family of drugs was experimentally synthesized in 1933; however, the tranquillizing effects of the benzodiazepines were not recognized until the late 1950s. At that time a new compound, chlordiazepoxide (e.g., Librium), was accidentally discovered to have a taming and quietening effect on previously vicious laboratory animals. In 1960, shortly after this serendipitous finding, the American Food and Drug Administration gave permission to Roche Laboratories to market the drug for clinical use. Three years later, diazepam (e.g., Valium) was introduced, and it is now the most widely prescribed drug in the world. Thereafter, several other members of the benzodiazepine family of tranquillizers were marketed in North America—oxazepam (e.g., Serax), chlorazepate dipotassium (e.g., Tranxene), lorazepam (e.g., Ativan), and nitrazepam (e.g., Mogadon); the last drug has been marketed in Canada only recently. None of these later benzodiazepines has achieved the enormous popularity of diazepam and chlordiazepoxide.

PHARMACOLOGICAL ACTIONS AND MEDICAL USES

The term “minor tranquillizer” is somewhat misleading; the pharmacological actions of these drugs are qualitatively rather than quantitatively different from those of the major tranquillizers, such as the phenothiazines, which are primarily used in the treatment of the psychoses.[22] In fact, the minor tranquillizers are generally not effective in modifying psychotic symptoms, irrespective of the size of the dose taken, although chlordiazepoxide is sometimes useful in controlling the agitation accompanying acute psychotic episodes.

Minor tranquillizers, particularly meprobamate, produce several effects which are similar to those produced by sedative/hypnotic drugs. For this reason, many researchers question whether the minor tranquillizers are a distinct class of drugs separate from the sedative/hypnotics. They argue that the differences between the two classes appear to be mainly quantitative rather than qualitative in nature. When administered in appropriate doses, drugs in both of these classes can effectively control anxiety, produce sedation and sleep, and control certain types of epileptic seizures. Nonetheless, the benzodiazepines clearly produce fewer and milder side effects in doses sufficient to manage anxiety or induce sleep; in contrast to the barbiturates, at therapeutic dose levels, the benzodiazepines do not affect respiratory functions; and even at very high doses their depressant effect on respiratory and cardiovascular functions tends to be significantly less than that of the sedative/hypnotics (barbiturates and similar drugs) and meprobamate. There is some evidence to suggest that the mechanisms of action of the benzodiazepines differ, to some extent, from those of the barbiturate-like drugs.

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[22] See the chapter on Mood Modifiers below.

Meprobamate offers no particular advantages over any of the benzodiazepines. At low doses, it effectively controls anxiety and reduces muscle tension; its typical side effects at such dose levels, sedation and drowsiness, tend to be less pronounced than those of barbiturate-like drugs. However, at moderate therapeutic doses, the side effects of meprobamate become more similar, and can include euphoria, motor incoordination, and mild cognitive impairment. At higher doses, the type of intoxication produced by meprobamate is almost identical to that produced by the barbiturates; while meprobamate tends to cause less respiratory depression than barbiturates, in severe overdose it can also produce stupor, coma, severely depressed reflexes, cardiovascular shock, and sometimes death, usually from heart failure. When an overdose is taken in combination with other CNS depressants, the probability of hazardous consequences greatly increases.

The benzodiazepines have a broader range of uses than meprobamate. Even at relatively low therapeutic doses, they can relieve anxiety, muscle tension, and fearfulness, and at these dose levels any adverse effects are infrequent and mild. When administered either orally or by injection, the benzodiazepines can also rapidly relieve more acutely severe conditions, such as extreme anxiety or panic reactions; in such cases, unwanted side effects are ordinarily not as pronounced as with the barbiturate-like drugs.

Diazepam, chlordiazepoxide, and oxazepam are clinically useful in reducing the severity of symptoms associated with acute alcoholic withdrawal. Diazepam is also widely used in relieving muscle spasms associated with certain types of physical disorders, such as cerebral palsy, and in controlling seizures and prolonged seizure activity (status epilepticus). Physicians also prescribe benzodiazepines to induce relaxation in patients whose anxiety or tension interferes with sleep. The drugs are also administered to hospital patients before a general anesthetic.

When taken in abusive doses, benzodiazepines can induce some of the behavioral manifestations associated with barbiturate intoxication, such as motor incoordination, slurred speech, confusion, and memory impairment.[23] However, only diazepam, and to a lesser extent chlordiazepoxide, produce euphoria.

Benzodiazepines are among the most commonly used drugs in suicide attempts because they are so widely prescribed for emotionally troubled patients. Fortunately, these drugs have a wide margin of safety; even when they have been taken in very large quantities, death resulting solely from benzodiazepine overdose is rare. However, when overdoses are taken in combination with other CNS depressants, the probability of lethal results is enhanced.

ABUSE AND MISUSE OF MINOR TRANQUILLIZERS

For several years following its introduction, meprobamate was widely thought to be harmless and to have little or no potential for abuse. Indeed, a key element in the marketing strategy was to emphasize the differences rather than the similarities between meprobamate and the barbiturates—that is, to persuade physicians that the long-desired alternative to the latter drugs was at hand. Meprobamate was undoubtedly useful to large numbers of patients who took it as prescribed; however, it was also widely misused and abused. For example, meprobamate is not appropriate in the management of depressive disorders, and those who decide on their own to take meprobamate for emotional depression may encounter an exacerbation of the depressive symptoms—sometimes resulting in suicidal behavior. Many patients once used this drug as a panacea even for the minor natural stresses of daily life.

Because meprobamate can produce barbiturate-like euphoria when taken at moderate to high doses (a phenomenon only belatedly recognized by most health officials), it was often substituted for or used in combination with alcohol or barbiturates. This practice appears to have been fairly widespread in North America; regular abuse for the purpose of euphoria resulted in several well-documented cases of severe physical dependence—another danger which many physicians and researchers originally minimized or believed was not possible. For these reasons, and because of the introduction of the safer benzodiazepines, the prescribing of meprobamate has rapidly declined since its peak use in the 1960s.

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[23] For some users, these symptoms can occur at lower doses.

The benzodiazepines were also originally believed to have little or no abuse potential. They are somewhat less desirable to the potential abuser than meprobamate or the barbiturate-like drugs, for none of the benzodiazepines generates the high level of euphoria associated with the latter drugs. Nonetheless, doses of diazepam beyond the therapeutic level can produce a degree of pleasurable intoxication sufficiently great to be attractive to street drug abusers. Diazepam (e.g., Valium) is the only minor tranquillizer which is at present widely available on the illicit street market; because it is easily available and inexpensive, it is often among the first of the psychoactive drugs to be encountered by those teenagers seeking drug experiences. It is also popular with heroin addicts and with patients in methadone maintenance programs; many in both groups have been known to take large quantities of diazepam either alone or in combination with other drugs in order to achieve a pleasant "high." Diazepam and chlordiazepoxide are prescribed for and abused by practising and recovered alcoholics; both of these drugs seem to potentiate the intoxicating effects of alcohol and other sedative/hypnotics. (In large doses these drug combinations can be hazardous.) Many abusers of hallucinogens and of stimulants also consume benzodiazepines mainly to combat the agitation and overstimulation caused by the former drugs.

Many experts believe that the benzodiazepines are greatly overprescribed. Their widespread availability unquestionably contributes to their abuse and misuse. For example, in the United States alone, over 70 million prescriptions are written each year for these tranquillizers. Physicians are more willing to prescribe them than sedative/hypnotics because they have such a wide margin of safety; as well, their propensity for producing physical dependence is not nearly as great as that of any of the sedative/hypnotics. Therefore, many busy physicians prescribe benzodiazepines in situations which would likely respond more favorably to brief counseling. Furthermore, it is not unusual for patients to be maintained on daily doses of one of these drugs for several months or years, without any other form of psychotherapeutic intervention; with such protracted use, benzodiazepines provide virtually no therapeutic value. Finally, as with meprobamate, benzodiazepines are not useful in treating disorders which are primarily depressive in nature, and, in fact, may cause such conditions to worsen.[24]

TOLERANCE AND DEPENDENCE

Tolerance develops to the psychoactive effects of meprobamate with regular use; therefore, ever-increasing daily doses are necessary in order to maintain the original intensity of desired effects. Physical dependence on this drug has been demonstrated to be related to the size of the daily dose. Mild physical dependence can occur with regular daily doses of 2.4 grams (2,400 mg). This amount is not substantially greater than the usual maximum therapeutic daily dose of 1.6 grams. When higher daily doses are taken, a severe barbiturate-like withdrawal syndrome can occur, occasionally resulting in death.

Tolerance to the anxiety- and tension-relieving effects of the benzodiazepines has also been demonstrated to develop when they are chronically used, even at therapeutic doses. Furthermore, chronic abuse in daily doses substantially in excess of the therapeutic range for any of these drugs can result in a state of physical dependence; symptoms of withdrawal can include agitation, abdominal discomfort, sweating, tremors, insomnia and other sleep dysfunctions, and loss of appetite. When withdrawal sickness occurs after abrupt termination of protracted use of extremely high doses, the syndrome can be severe; however, although symptoms may include delirium and grand mal seizures, no deaths have been reported.

Psychological dependence on the minor tranquillizers is undoubtedly widespread. These drugs have come to be used for such a variety of stressful conditions that many people believe they cannot function without them.

[24] However, in combination with antidepressants, benzodiazepines can be effective in treating nonpsychotic conditions characterized by agitated depression.

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Hallucinogens

See the articles in section 3 on the following substances: cannabis, LSD (lysergic acid diethylamide), mescaline, MDA (methylenedioxyamphetamine), PCP (phencyclidine), PMA (paramethoxyamphetamine), and psilocybin. See section 4 for articles on *Amanita muscaria* (fly agaric), atropine and related alkaloids, DMT (dimethyltriptamine), harmaline, ketamine, morning glory seeds, nutmeg, peyote, STP (DOM), and TMA (trimethoxyamphetamine).

Hallucinogens include a wide variety of structurally dissimilar substances, ranging from wholly synthetic products to substances naturally occurring in many plant species throughout the world.[1] Typical doses of most hallucinogens can produce a spectrum of vivid sensory distortions and also markedly alter mood and thought. Users most frequently experience visual distortions, but any of the other sensory modalities (hearing, smell, taste, touch) can also be intensely affected. Furthermore, the individual's perception of time, of the external world, and even of self can be dramatically changed.

The effects produced by any hallucinogen and the subjective reaction to those effects can differ significantly among individual users and may range from ecstasy to terror. In fact, during any one hallucinogenic episode a user is likely to experience various psychic and emotional reactions. As well, any hallucinogen in its pure form can also induce varying experiences, in exactly the same dose in the same user, from one drug-taking event to the next.

In addition to the pharmacological properties of any hallucinogenic substance, other variables which can influence the user's response include size of dose taken, attitudes and expectations, previous experiences with hallucinogens, setting or context in which the drug is taken, the user's personality, and emotional state at the time of taking the drug. Therefore, predicting a given user's responses during a specific drug-taking episode is uncertain, for even a regular user with a highly positive attitude can on occasion experience unexpected and intensely unpleasant effects. These factors make it more difficult to generalize about the hallucinogenic experience than about experiences resulting from any other class of psychoactive drugs.

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[1] Most naturally occurring hallucinogens can also be synthesized in laboratories.

HISTORY OF HALLUCINOGEN USE

The earliest recorded use of hallucinogenic substances for their intoxicating effects is found in India in ancient Vedic writings, dating back to approximately 1600 B.C. Use of the mysterious and supposedly divine "soma" is celebrated in the hymns of the Rig Veda; these hymns, written in Sanskrit, are among the earliest foundations of the Hindu religion. One in 10 of the over 1,000 hymns directly refers to and deifies a plant able to produce altered states of consciousness, now believed (on the basis of strong research evidence) to be the fly agaric mushroom, *Amanita muscaria.*[2]

A similar ancient tradition of religious (and in this case also therapeutic) use can be traced for *Cannabis sativa* and its constituents, marijuana and hashish. Evidence of cannabis use for its mood-altering properties was recorded in ancient China and is also found in the works of the early Greek writer Herodotus (5th century B.C.). Two well-known researchers in the field of hallucinogens, R. Gordon Wasson and Albert Hofmann (1978), and a student of classical Greece, Carl A.P. Ruck, also present compelling arguments concerning the secret ritual use of lysergic acid alkaloids (obtained from ergot-infected grain) in ancient Greece.

Various flora of the Solanaceae (potato) family[3] containing one or more of the hallucinogenic alkaloids atropine, scopolamine, and hyoscyamine have been used for centuries. They are known to have been used in such ancient cultures as Greece, Rome, Assyria, Persia, Egypt, Hindu India, and China—not only in religious rituals but also in medicine, sorcery, and magical applications, probably for prophecy and divining and not infrequently as poisons. These substances were used in Europe during the late Medieval period and the Renaissance, times of widespread witchcraft and demonology. The strange visions and bizarre behavior induced by them were taken as proof of contact with the forces of Satan.

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[2] Some researchers have speculated that fly agaric was probably in use before recorded history; in fact, it continues to be ritually used in such remote areas as Northeastern Siberia.

[3] E.g., several species of datura, belladonna, mandrake, and henbane.

In contrast to the Eastern Hemisphere, where only about a dozen species of plants contain hallucinogenic alkaloids, there are over 90 such species (known) in the Western Hemisphere; a number contain atropine and scopolamine (Grinspoon & Bakalar, 1979). Evidence suggests that many Indian tribes of both North and South America and the West Indies used hallucinogens mainly for ritual and medicinal purposes long before the intrusion of the Europeans. Huge carved "sacred mushroom" stones were recently discovered in a remote area of Guatemala; the stems appear to be the head, and some cases the entire figure, of a god. Archeologists believe that they are over 3,000 years old, greatly predating the Mayan civilization in this area. Chroniclers of Columbus's second voyage wrote of a snuff widely used by the natives of the West Indies that was alleged to induce visions and was used on purely social occasions as well as in religious ceremonies. It is believed that this snuff was obtained from the plant *Piptadina peregrina*, which contains the moderately potent hallucinogen DMT (dimethyltriptamine).

Some cultures, such as the Mayan and Aztec, not only used hallucinogens for centuries but also cultivated plants which produced them; among these was the vine-growing morning glory *Rivea corymbosa*, the seeds of which contain the alkaloid d-lysergic acid amide.[4] Other cultivated plants included "sacred mushrooms" (belonging to the genus *Psilocybe*), which contain the hallucinogens psilocybin and psilocin, and such varieties of the peyote cactus as *Lophophora williamsii*, in which mescaline is found.

Unlike Pizarro and his successors, who permitted the conquered natives of Peru to continue using coca leaves (the source of cocaine), their fellow conquistadors in Mexico attempted to eradicate all use of hallucinogens. However, in spite of severe treatment by the Spanish invaders, secret Indian sects continued to use hallucinogens in their rituals. In the 19th century, raiding Mescalero Apaches (from whom mescaline derives its name) adopted the peyote ritual from northern Mexican tribes. Its use then rapidly spread to other Indian tribes in the western United States and even in Canada.

In 1918 the Native American Church was incorporated, with a

[4] Many of the effects of this substance (LSA) are similar to those produced by LSD.

following composed entirely of members of Indian tribes. After several court battles, this body was finally granted the right to use peyote as a sacrament in religious rituals in the United States. This is now the only legally approved use of any major hallucinogen in North America outside of research.[5]

Among other North Americans and Europeans, hallucinogens did not achieve broad popularity until the past few decades. Several theories have been advanced to explain the dramatic discovery and subsequent widespread use among young people of these substances during the 1960s, when LSD and cannabis were in the vanguard and achieved the greatest popularity of the hallucinogenic drugs. From the beginning of the 1960s to the early 1970s was a period of deep division in American (and to a lesser extent Canadian) society between a large segment of the youthful population and the adult population. Many young people rejected traditional values in favor of experimentation with new ideas and values; among these ideas was experimentation with drugs, a practice generally disdained by the adult population. However, many folk heroes of that time—including pop singers and some respected intellectuals, most notably the Harvard professors Timothy Leary and Richard Alpert—gave open support to the use of hallucinogens. That these drugs are also illegal probably served as an additional incentive to many young people in their defiance of the older generation. Nonetheless, it should be kept in mind that only a fraction of young people regularly used hallucinogens, and recent surveys suggest that most of these users stopped the practice and became only occasional or infrequent users of cannabis.[6]

HALLUCINOGENIC ACTIONS

Class Designations Derived from Drug Actions

The terms "hallucinogen," "psychotomimetic," and "psychedelic" have often been used interchangeably as designations for most or all of the members of this class of drugs; however, none of their literal definitions satisfactorily embraces the wide variation of effects the drugs produce.[7] Nonetheless, these are the terms now generally used to signify substances that consistently produce changes in thought, perception, and/or mood, usually without causing serious disturbances in the autonomic nervous system (when taken at typical doses) or creating such other problems as serious dependence. "Hallucinogen" is the most widely used term of the three; thus, for our purposes it will be the only one employed.

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[5] Although there are branches of the Native American Church in Canada, the legal right of its members to use peyote has not been established.

[6] However, in spite of an overall decline in the use of hallucinogens among today's young people, marijuana continues to be increasingly popular. Still, some very recent survey evidence suggests a leveling off in the prevalence of cannabis use among high school students.

Classes of Hallucinogens[8]

The LSD Family: Known as indolealkylamines, this family bears a similarity to 5-hydroxytryptamine, a transmitter substance found in the brain. Important members include LSD (d-lysergic acid diethylamide), LSA (d-lysergic acid amide, found in the seeds of several varieties of morning glory), psilocybin, and DMT (dimethyltriyptamine).[9] LSD is a semisynthetic substance derived from ergot, a fungus which grows on certain grains such as rye. LSA, psilocybin, and DMT are entirely natural alkaloids. All can be synthesized in a laboratory.

Shortly after ingestion, these drugs can produce a variety of physical symptoms, which include increased heart rate and blood pressure, elevated body temperature, reduced appetite, nausea, vomiting, abdominal discomfort, rapid reflexes, motor incoordination, and pupillary dilation.[10] At typical doses for each of these drugs (except for DMT) most of these effects tend to be mildly to moderately intense;

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[7] "Hallucinogen" literally means hallucination-producing. However, hallucinations are not the main effect of several of these drugs; in the case of some, they occur only at doses substantially higher than typical amounts taken by users. The terms "psychotomimetic" and "psychotogenic" have meant, respectively, mimicking natural forms of psychosis and psychosis-producing; however, there are too many important differences between the states produced by these drugs at typical doses and naturally occurring psychotic states for the definitions to be accurate (although high doses of some of these drugs can produce toxic psychotic effects in users). The term "psychedelic," coined by the psychiatrist Humphry Osmond, originally meant mind-revealing or mind-manifesting; it has also come to mean the propensity of some of these drugs to give rise to alleged mystical (or transcendental) states.

[8] According to structural similarity.

[9] Other members of this family, rarely found on the North American illicit drug market, include harmaline, ibogaine, DET (diethyltryptamine), and DPT (dipropyltriptamine).

[10] Many of these effects may also be mildly depressed (that is, functioning at levels below normal for the user) later in the same episode.

with DMT, the physical effects tend to be more intense and more rapidly experienced.[11]

The intensity of hallucinogenic effects of the major drugs in this family is related to size of dose: that is to say, with increasing doses, changes in effects are usually of a quantitative rather than qualitative nature. Distortions of any of the sensory modalities can occur with any of these drugs, although visual distortions are the most common. At typical doses, users are likely to perceive a kaleidoscope of visual patterns and objects which they know are not real ("pseudohallucinations") as well as changes in the size, shape, distance, etc. of objects which they also know are not really occurring ("pseudoillusions"); however, even at low doses, such effects can appear quite real to a minority of users. Distortions of time, space, and body image frequently occur, and recognized boundaries between self and the environment may temporarily seem to change and possibly even to disappear. Synesthesias—the melding of two sensory modalities (e.g., music being "seen")—are also common.

In addition, these drugs can markedly affect thought processes and memory. It is not unusual for short-term memory (i.e., of immediately prior events) to be impaired, while at the same time distant and forgotten events may be vividly recalled. In fact, recall can be so greatly affected that the person may not be able to discriminate between past and present. Users may also accord heretofore trivial matters or objects new importance and meaning, and they may believe that they are undergoing a profound mystical or religious experience.[12]

The above effects and emotional reactions to them vary greatly among users. The desired reactions are, of course, joy and ecstasy, and many users achieve these states. However, users may also experience transient periods of fearfulness and anxiety during the course of the same hallucinogen-taking episode. Some users encounter only adverse effects on a given occasion, particularly those who have had few or no previous experiences with hallucinogens. When prolonged periods of highly unpleasant emotions (which can range from persistent anxiety to terror) dominate the episode, the person is said to have undergone a

[11] In fact, all of the effects of DMT disappear much more rapidly than those of other members of this family of substances, usually within 30-60 minutes after ingestion.

[12] It is exactly this latter effect that caused psilocybin to be so greatly revered by many pre-Columbian tribes in Mexico and Central America.

"bad trip." These effects usually disappear after the drug is metabolized and excreted.[13] Among drugs in this family, DMT most frequently induces agitation and nonpsychotic panic states. The major factor contributing to the increased risk with DMT is likely the short lapse of time between ingestion and peak experience of hallucinogenic effects, ordinarily 10–20 minutes after administration; apparently the user needs a gradual psychic readjustment from the drug-free state. With other members of this family of drugs there is a considerably longer period of time before onset of hallucinogenic effects.

DMT and harmaline are monoamine oxidase inhibitors (i.e., they block the availability in the body of MAO, an enzyme which metabolizes norepinephrine and related compounds). MAO inhibitors can interact with a variety of drugs and constituents of foods (such as those in red wine and aged cheese) to produce hazardous and sometimes lethal results.[14]

Mescaline and MDA: Mescaline and MDA (3,4-methylenedioxyamphetamine) are the only members of the phenylethylamine group of drugs to have achieved at least moderate popularity among hallucinogen users in some North American locales. (They are encountered only very rarely in Canada.) Others which have at least occasionally been taken by street drug users during the past decade include PMA (paramethoxyamphetamine), DOM (also known as STP[15]—2,5-dimethoxy-4-methylamphetamine), TMA (trimethoxyamphetamine), and MMDA (3-methoxy-4,5-MDA).[16] Mescaline is the only entirely natural alkaloid in this drug family, and it, too, can be synthesized.

Most phenylethylamines share the psychoactive effects produced by the LSD family of hallucinogens.[17] For example, though it is considerably weaker than LSD in equal doses, mescaline produces almost identical sensory and psychological effects. However, it cannot be used to prolong the hallucinogenic effects of LSD once the effects of the latter drug are attenuated by the development of tolerance.

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[13] The subject of adverse effects is more generally explored later under Abuse of Hallucinogens.

[14] See article on Monoamine Oxidase Inhibitors in section 4.

[15] The origins of "STP" are unknown. Some claim that the name is an abbreviation for serenity, tranquility, and peace, while others claim that because of this drug's potent amphetamine-like effects at higher doses, it takes its name from the motor oil additive.

[16] This last substance can be produced from the main psychoactive principle of nutmeg, myristicin.

Phenylethylamines bear a close structural relationship to the amphetamines. At high does, therefore, these drugs can produce agitation and marked stimulation of the peripheral nervous system, manifested, for example, in both abnormally accelerated heart rate and very high blood pressure. The parallel extends further in that amphetamines will also produce hallucinations at sufficiently high doses.

Because of the simple molecular structure of the phenylethylamines, it has become a simple matter to produce a large number of derivatives with varying degrees of effects. This fact has led to a number of drug-abuse crises, the most notable involving the creation and use of the drug PMA. A few years ago, PMA was synthesized in illicit laboratories and sold on the street as MDA. Unfortunately, the slight modification of chemical structure that produced PMA had extreme consequences for some users, who were expecting the effects of a typical dose of MDA. PMA's heightened stimulant properties caused hypertensive crisis and convulsions and, in numerous cases, death.

TMA also produces some unusual effects as the size of the dose is increased, although these effects are not nearly so hazardous as those produced by PMA. The mescaline-like effects observed at lower doses of TMA tend to be replaced at higher doses by such behavior as unprovoked anger and aggression.

Like most members of the LSD family, most drugs in the mescaline family are produced only for the street user in illicit laboratories; the small quantities legally produced are for research purposes.[18] Frequently, illicit manufacturers know very little about the possible outcome of use of these new substances; moreover, the drugs are often adulterated with other substances which in themselves may cause serious medical problems for the user. Nor is the manufacturer under pressure to provide consistent quality and purity. Recreational use of drugs in this category is therefore a particularly risky venture.

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[17] However, at typical doses, MDA ordinarily produces a pleasant state of peacefulness and relaxation with few hallucinogenic effects. Moderately high doses produce LSD-like effects. At still higher doses, MDA can produce extreme CNS excitation, occasionally with fatal results.

[18] However, psilocybin and mescaline can be obtained in some areas from the *Psilocybe* mushroom and the peyote cactus respectively.

Finally, drugs in this group are quite frequently subject to misrepresentation on the street. MDA and mescaline, for example, are seldom available; yet hundreds of samples of drugs come into street-drug analysis centres every year labeled mescaline and MDA. In the vast majority of cases the drugs are actually PCP, LSD, or the two combined along with psychoactively inert substances.

PCP and Ketamine: Two dissociative anesthetics, phencyclidine (PCP) and ketamine, belong to the arylcycloalkylamine family of drugs. PCP can produce such a spectrum of effects that it is difficult for users to predict what they will experience from one drug episode to another or indeed within a single episode. PCP and ketamine both produce hallucinogenic effects at relatively low dose levels. PCP has been shown to produce stimulant effects, depressant effects, analgesic effects, anesthetic effects, and hallucinogenic effects, depending on the dose level, the user, and the situation in which the drug is taken.

The particular combination of effects that a PCP user experiences seems to be somewhat dependent on dose levels. For example, certain effects on the autonomic system at low dose levels can mimic those of stimulants (e.g., increased heart rate and elevated blood pressure), while muscular incoordination and impaired respiration mimic the effects of depressants. As the dosage increases, both the stimulant and depressant effects become more severe: there may be a dangerous fall in blood pressure and heart rate at one point, and at another point the user may be suddenly and dramatically stimulated into convulsions, coma, and death.

Less close scientific study has been made of the side effects of high doses of ketamine; yet early indications suggest that ketamine may also produce many of the disorienting and paradoxical stimulant/depressant effects of PCP. Even at low to moderate dose levels, both drugs can create delusions and mental confusion progressing to hallucinations and degrees of dissociation bordering on schizophrenic states.

PCP is the most common hallucinogen found on the street drug market after cannabis. In fact, in 1975 in the Drug Analysis Unit of the Addiction Research Foundation, all of the samples of drugs that had been sold as mescaline, peyote, or THC proved to be PCP or some combination of PCP and another drug.

The PCP story began in the 1950s when one pharmaceutical company (Parke Davis) experimented with it as a general anesthetic. The company was preparing to market PCP for human use when it discovered at the clinical experimentation stage that the undesirable possible side effects include such severe consequences as convulsions during surgery and delirium, confusion, visual disorientation, and hallucinations as the drug begins to wear off. A decade later, PCP was easily available to street drug users in San Francisco,[19] and during the 1970s abuse became widespread throughout North America.

The history of ketamine is less checkered to date. It is still in use as a general anesthetic in spite of its dissociative and hallucinogenic side effects. Abuse appears to be on the upswing in the United States, although it does not yet seem to have spread to Canada.

Marijuana and Hashish: Cannabis sativa contains as its principal psychoactive constituent THC (Δ^9-tetrahydrocannabinol),[20] the most enduringly popular hallucinogen. Marijuana is prepared from the flowering tops and leafy material of the plant and often contains such natural adulterants as stems and seeds; in North American street samples of marijuana cigarettes, the amount of THC usually ranges from 1% to 5% of the bulk weight. Hashish is a combination of the dried resinous exudate and the compressed flowers obtained from the female plant;[21] the THC content of street samples of hashish ranges between 4% and 10% of the bulk weight. (These figures are highly variable because of frequent shifts in sources.) The viscous and much more potent oil of hashish is obtained by boiling hashish in an appropriate solvent such as ethyl alcohol and then filtering the sediment or waste; the resulting yield of THC usually ranges between 10% and 30% of the remaining bulk, although samples containing up to 60% THC have been reported. Pure THC is almost never found on the street, although several substances, such as PCP and low-grade cannabis products, are often misrepresented to be pure THC.

[19] It was also reintroduced as an anesthetic and tranquillizer in veterinary medicine.

[20] THC can also be synthesized in the laboratory, but the process is both expensive and difficult.

[21] Cannabis is "dioecious"—i.e., there are both male and female plants of this species.

Cannabis use is a phenomenon spanning the drug-use history of many cultures and thousands of years. Unlike many of the natural hallucinogens mentioned earlier, cannabis seems to grow in many climates, is very easy to cultivate, and retains its psychoactive properties wherever it is grown. Efforts to restrict its availability are thus almost impossible. Although cannabis is not native to North America, it can be easily grown in most parts of Canada, the United States, and Mexico.

At low to moderate doses, cannabis produces relatively mild and transitory physical symptoms, which can include increased heart rate, muscle weakness, mild motor incoordination, slight tremors, reddened eyes, involuntary movement of the eyeballs, slightly increased body temperature, increased appetite, and dry mouth and throat. In this dose range, most users experience euphoria, disinhibition, relaxation, and garrulousness; however, drowsiness and sedation often follow the initial stimulation and exhilaration. Hallucinogenic effects are generally dose-related and relatively mild, although the range and intensity of effects varies greatly among users. Typical doses of cannabis (such as a few milligrams of THC in a marijuana cigarette) produce perceptual distortions in some users. Higher doses in most users produce LSD- or mescaline-like changes in perception and thought. Vivid visual imagery is much less commonly experienced than with most other hallucinogenic drugs, and the psychoactive effects tend to disappear more rapidly, typically within one to two hours after smoking.

Cannabis can also cause unpleasant effects in some users, although these seem to occur less frequently and generally with less intensity than with other hallucinogens. In low to moderate doses, mild to moderate anxiety may be experienced, most commonly among inexperienced users. More severe consequences occasionally occur at higher doses and less frequently at lower doses; these may include severe anxiety, panic reactions, paranoid thinking, and frightening hallucinations.

The Atropinic Family: The atropinic drugs, atropine, scopolamine, and hyoscyamine, are also collectively designated solanaceous alkaloids because they are found in many species of potato plants (Solanaceae). All three of these substances (plus other chemically related alkaloids) are found in the plants *Atropa belladonna*[22] (deadly nightshade), *Datura stramonium* (jimson weed), and several related species throughout the world.

[22] Hence they are also widely referred to as the belladonna alkaloids.

These drugs have been subject to relatively infrequent street abuse in North America, although they are available in numerous medications for symptomatic relief of a variety of medical problems. At therapeutic dose levels,[23] scopolamine taken orally is the only one of them that produces psychoactive effects of abuse interest such as mild euphoria, sedation, and drowsiness. At higher doses,[24] all of them can produce intense central and peripheral effects, including any of the following:

1. Central: visual, auditory, and tactile hallucinations; visual illusions; severe disorientation and confusion; memory loss; paranoid thinking; agitation; articulation difficulties and significantly impaired motor coordination; maximal dilation of the pupils; and convulsions.
2. Peripheral: rapid and weak pulse, abnormally rapid and irregular heart rate, and abnormally high blood pressure; headache; fever; dry and burning sensations in the mouth; nausea and vomiting.

The entire episode may last for 24–48 hours, as compared with 6–12 hours with LSD; psychic effects have been known to last for several days.

MEDICAL USES

Very few hallucinogens are currently used in clinical medicine. Ketamine is employed as an intravenous anesthetic in many surgical procedures when the use of an anesthetic mask is undesirable, as with operations involving the head and neck.

The atropinic alkaloids have been used to control smooth-muscle spasms (as antispasmodics), hyperirritability of the gastrointestinal tract, excessive salivation and bronchial secretions, and parkinsonism. They are also employed in topical solutions to produce pupillary dilation for certain kinds of eye examination and to combat some types of inflammation of the eye. Scopolamine is used to control motion sickness.[25]

[23] 1 mg or less.

[24] 10 mg or more.

[25] Over-the-counter scopolamine preparations used in the past in Canada specifically to produce drowsiness and sedation have been replaced by products containing an antihistamine. For motion sickness scopolamine is currently available for transdermal application (i.e., absorbed into the body through the skin).

Several potent hallucinogens, most notably LSD, were explored in the past as adjuncts to traditional psychotherapy, in the treatment of alcoholism, and in a variety of other interventions related to emotional problems. However, experimentation for such purposes has now generally been discontinued, for there was insufficient evidence of therapeutic efficacy to justify the use of such potent and potentially disruptive agents in human subjects.[26] Nonetheless, some researchers continue to believe that experimentation was prematurely abandoned and have urged that further investigations be undertaken.

EFFECTS OF HALLUCINOGEN ABUSE

Acute Adverse Episodes

Virtually all of the hallucinogens can produce adverse effects. In most cases, these consequences tend to be manifested as relatively mild and transient feelings of physical discomfort, anxiety, and/or depression. Such symptoms occur routinely, even during otherwise enjoyable hallucinogenic episodes. However, more severe adverse consequences can occasionally occur and with abrupt onset even in regular users who have had no prior negative hallucinogen-related experiences. These are most frequently experienced as intense anxiety, panic, or paranoid states. The most extreme severe reaction, toxic psychosis, occurs relatively infrequently at typical hallucinogenic doses; the syndrome ordinarily includes true hallucinations, delusional thinking, confusion, disorientation, and bizarre and sometimes violent behavior. In most cases, the psychosis clears within anywhere from a few hours to a few days; however, it may persist in some individuals for several months.

With many hallucinogens (e.g., the atropinic alkaloids, PCP, and MDA) the most important factor contributing to a severely adverse reaction—the "bad trip"—is the size of the dose; nonetheless, a user may suffer an extremely unpleasant episode on any given occasion, irrespective of the size of the dose. Little is known about which other factors can precipitate such acutely adverse episodes, or why they occur on some occasions and not on others, or indeed why some individuals appear to be more vulnerable to them than others. It would seem plausible that the user's personality, current emotional state, past hallucinogen experiences, attitudes, and the setting in which the hallucinogen is taken are likely contributing factors; however, none of these variables has been empirically demonstrated to increase significantly the probability of a severely adverse episode.[27]

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[26] The exception is cannabis, which is currently being investigated for possible clinical use in the treatment of a few medical disorders. See the article on Cannabis in section 3.

Reliable reports of bizarre crimes of violence, homicides, suicides, and self-mutilations directly associated with the use of hallucinogens are uncommon, although unsubstantiated rumors are abundant. In fact, given the literally millions of unremarkable hallucinogenic episodes, the lack of documentary evidence would suggest a very low frequency of violent events. In those instances when violence has occurred, the hallucinogens most frequently implicated are PCP and LSD. Case histories of dangerously violent behavior indicate that severe paranoia or some other drug-induced psychotic manifestation was involved and that the individual was usually a regular user of PCP or LSD.

The known incidence of hallucinogen-related serious accidents and accidental deaths also appears to be relatively low. For other than vehicle accidents (which tend to implicate cannabis), PCP and LSD are the hallucinogens most frequently associated with serious and lethal accidents. Little documentation is available concerning the incidence of cannabis-related vehicle accidents. Indeed, there may be a significant hidden problem, particularly since cannabis is so widely used in our society. It has been clearly established that even low doses of cannabis can impair driving performance under a variety of standard conditions. Unfortunately, at this time there is no simple test comparable to the Breathalyzer which can be easily administered to drivers to determine the amount of cannabis in the body.

Deaths from acute overdose have been known to occur with some hallucinogens. Fortunately, the two most widely used (cannabis and LSD) are not known to have directly caused any deaths even at extremely high doses; nor have mescaline and psilocybin. Certain other hallucinogens, however, are highly toxic. In fact, atropine, scopolamine, and hyoscyamine are so dangerous at very high doses that plants containing high concentrations were specifically used for centuries as poisons in Europe and parts of Asia. PMA has also proven to be highly lethal. Other hallucinogenic substances which are known to have

[27] No specific user variables have been clearly demonstrated to induce acute toxic psychotic episodes. However, when this disorder persists for long periods of time, the probability is that the individual involved was a latent psychotic or was otherwise severely disturbed prior to the psychosis-inducing event.

caused deaths from overdose include fly agaric, nutmeg, ibogaine, PCP, and MDA.

Flashbacks

The spontaneous, transitory, and drug-free recurrence of feelings, perceptions, and thoughts which were originally experienced during a hallucinogenic episode is a relatively common event among users; this experience is called a flashback. Various studies have reported flashback experiences among up to 25% of users (but most studies report lower rates). Although primarily associated with LSD, flashbacks can occur with other hallucinogens.

Visual flashbacks tend to be the most common, although other sensory flashbacks may occur. For example, recurrence of specific intense feelings, spontaneous recall of forgotten thoughts, distortions of time, body image, and reality, or almost any other experience originally occurring during a hallucinogenic "trip" can unexpectedly recur, and the individual's subjective reaction may range from intense pleasure to terror. Usually these experiences are brief, lasting no more than a few seconds to a few minutes; however, on rare occasions they have been known to last for considerably more extended periods of time, up to several hours. Regular users are more likely to experience flashbacks than those who have undergone only one or two LSD episodes. A particular flashback may occur only once or may occur repeatedly over a period of several months.

It is not yet possible to predict the conditions generally conducive to the occurrence of flashbacks. Depending on the individual, flashbacks may occur during periods of either stress or relaxation, while under the influence of cannabis or alcohol or in a drug-free state, and while dreaming or while awake. The cause of the flashback phenomenon is not known; although many physiologically based hypotheses have been suggested, none have been empirically confirmed.

Amotivational Syndrome

The term "amotivational syndrome" designates a collection of certain characteristics and behaviors reported to be manifested by some chronic heavy users of hallucinogens, mainly of cannabis and LSD. The most commonly reported symptoms are gradually increasing apathy and decreasing interest in both environment and social contacts, loss of effectiveness, passivity, diminished frustration tolerance, lack of interest in planning ahead, and disregard for typical social conventions such as appropriateness of dress and public comportment.

Since some hallucinogen users have been known to manifest many or all of the above symptoms, a causal relationship between the use of hallucinogens and the syndrome has been postulated, although not adequately demonstrated. An alternative explanation is that the amotivational syndrome was simply part of a lifestyle adopted by many young people during the 1960s and early 1970s. Conservatively, it may be suggested that in some respects the use of cannabis, LSD, and other hallucinogens may serve to foster an amotivational syndrome in certain individuals, and perhaps for some others the amotivational syndrome as a lifestyle may serve to foster the use of hallucinogens.

Organic Impairment

Psychological and neurological tests designed to detect organic brain impairment have failed to reveal any consistent and statistically significant differences between small groups of healthy nonusers and regular users of LSD. Findings of chromosomal damage in users of LSD and cannabis have been inconsistent; thus no firm conclusions can be drawn from available evidence.[28] Even in those cases where chromosomal damage has been reported, its significance is not known. Some research studies have found a higher risk of both spontaneous abortion and congenital abnormalities in the offspring when mothers regularly used LSD during their pregnancy; however, even these findings must be interpreted with caution, as almost all mothers in these studies also used other drugs during their pregnancy.

Nonetheless, it must be kept in mind that almost all of the above findings are preliminary and that well-controlled short-term and longitudinal studies in these areas are few in number.

TOLERANCE AND DEPENDENCE

The members of the LSD family of hallucinogens (except for DMT)[29] produce a form of rapidly developing tolerance that is more correctly referred to as tachyphylaxis. Psychoactive effects, after repeated daily administrations over as little as three to four days, will no longer be experienced irrespective of the dose. In other words, in contrast to many other drugs of abuse, dose increases cannot be used to maintain the desired original effect (or compensate for acquired tolerance). Original sensitivity is restored only after a several-day period of abstinence. Cross-tachyphylaxis also operates among drugs within this family;[30] after the user can no longer achieve the effects produced by one member of this family of substances, insensitivity to the psychoactive effects of other members will also occur until after the minimum period of abstinence.

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[28] One recent study compared the rate of chromosomal abnormalities among Mexican Indians who had ritually used peyote for generations with the rate among those who did not use peyote. The authors reported no differences in rate between the two groups. See the article on Mescaline in section 3.

[29] The only study exploring tolerance to the effects of DMT found considerable variation among subjects in the degree to which they had developed tolerance after daily administrations for several days.

Physical dependence on any of the LSD family is not known to occur, although psychological dependence on LSD has been reported to occur occasionally.

Except for mescaline, little is known regarding the tolerance- and dependence-producing properties of the members of the phenylethylamine family of hallucinogens. In the case of mescaline, not only does tachyphylaxis occur, but mescaline also shares cross-tachyphylaxis with some members of the LSD family, including LSD and psilocybin. There is no evidence that physical dependence on mescaline can develop.

Tolerance to the effects of phencyclidine (PCP) has yet to be clearly demonstrated. However, preliminary investigations of chronic users suggest that, given daily administration, frequent dose increases over several weeks are required to sustain the intensity of effects desired. Physical dependence has not been observed in either animals or humans; however, psychological dependence has been reported in chronic heavy users.

Short-term reverse tolerance can be created by cannabis, uniquely among hallucinogens. That is, for a relatively brief period users actually become increasingly sensitive to the desired effects.[31] Nevertheless, tolerance develops with regular use, and ever greater doses are then required to produce the original intensity of pleasurable effects.

In contrast to other hallucinogens, there is also some research evidence indicating physical dependence on cannabis with chronic high-dose use. Abrupt discontinuation may result in mild withdrawal symp-

[30] Recent evidence indicates that LSD and DMT do not share cross-tachyphylaxis.

[31] See cannabis article for discussion of reverse tolerance.

toms: irritability, sleep disturbances, weight loss, inhibition of appetite, sweating, and gastrointestinal upsets. Psychological dependence on cannabis also appears to occur in some users.

Tolerance to the effects of the atropinic alkaloids develops to a limited extent in humans; however, these drugs do not appear to produce dependence.

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Mood Modifiers

Major Tranquillizers and Antidepressants

See the articles in section 3 on the phenothiazines (e.g., chlorpromazine) and the tricyclic antidepressants (e.g., Elavil). See section 4 for articles on haloperidol (Haldol) and the monoamine oxidase (MAO) inhibitors (e.g., Parnate).

Mood modifiers are found in the middle range of drugs midway between the stimulants such as amphetamines and the depressants such as sedative/hypnotics. Stimulants and depressants exert effects on the brain of increased and decreased levels of activity respectively. Mood modifiers, on the other hand, produce a broader spectrum of effects. Drugs in this group include mood elevators or antidepressants and major and minor tranquillizers. The minor tranquillizers are discussed above in the chapter on CNS depressants, because their drug actions more closely resemble those of the sedative/hypnotic drugs than of the major tranquillizers.

MAJOR TRANQUILLIZERS

In this classification, the term “major” does not refer to the relative potency per se of the preparations, but rather to the types of psychiatric illnesses for which they are clinically indicated—that is, many forms of psychosis and severe neurotic agitation and anxiety.

A few years after the antihistamines had been developed in the late 1930s, it was reported that they had a quietening effect on patients suffering from severe psychiatric disorders. Until then it had been necessary to treat these patients with very heavy doses of such sedative/hypnotic drugs as bromides and barbiturates, which often rendered them insensible and unable to carry out all but routine functions. Therefore, the introduction of antihistamines represented a significant step in the treatment of psychotics, as a number of brain activities suppressed by the sedative/hypnotics remained unaffected by antihistamines. Chemists soon found that by manipulating the formula of the antihistamines they could reduce the amount of antihistamine activity and increase the potency of the calming or tranquillizing activity. The tricyclic major tranquillizers, known as the phenothiazines, were the product of this chemical search; chlorpromazine, the prototype, was synthesized in 1950.

Early clinical application of chlorpromazine to psychotic patients indicated that it had a broad range of desirable effects: for example, a calming effect on hyperexcited patients; increased alertness and activity in withdrawn, apathetic, or lethargic patients; reduction of fearfulness and even of terror associated with hallucinations; and reduction of distressing delusional thinking. Unlike the barbiturates, chlorpromazine in doses sufficient to produce sedation usually results in relatively little muscle weakness or incoordination, and, if sleeping, the patient is fairly easily aroused.

While sedative effects are often readily observed after initial administration, the antipsychotic (tranquillizing) effects of phenothiazines occur more gradually, and it may take up to several weeks before the patient appears to have noticeably improved. Tolerance to the sedating effects develops gradually; however, tolerance to the antipsychotic effects ordinarily does not occur to any appreciable extent. It is uncertain whether chronic use of phenothiazines produces physical dependence. An infrequent withdrawal syndrome has been reported, consisting of a rebound of psychotic behavior temporarily worse than that prior to drug therapy, muscular discomfort, and sleeping difficulties. The major tranquillizers have little or no abuse potential; however, deaths have been known to occur when patients combine them with large doses of alcohol, barbiturates, or other CNS-depressant drugs.

Some scholars point to the introduction of chlorpromazine in the early 1950s as the major breakthrough in the field of psychopharmacology. It has been observed that chlorpromazine had as significant an impact on the major mental illnesses as the penicillins had on the major infectious diseases. However, chlorpromazine and its many analogues do not cure mental illness; their contribution is rather in the management of the symptoms of psychosis, permitting patients to engage in other therapeutic endeavors and to live more productive lives in their community. Prior to the introduction of major tranquillizers, most psychotic patients admitted to mental hospitals became either permanent or long-term residents. Since then, there has been a dramatic decrease in the number of chronic residents in the mental hospital population and fewer hospital admissions and readmissions.

MOOD ELEVATORS (ANTIDEPRESSANTS)

A very slight modification of the tricyclic phenothiazines has yielded a group of compounds referred to as mood elevators or tricyclic antidepressants. Although the first, imipramine (e.g., Tofranil), was synthesized in 1948, its mood-altering actions were not discovered until almost a decade later (1957). Shortly thereafter, the most widely employed drug in this case, amitriptyline (e.g., Elavil), was introduced. In fact, while there are a variety of available mood elevators such as the MAO inhibitors (see article in section 4), the tricyclic antidepressants have become by a wide margin the most popularly prescribed. There are close to 25 million prescriptions written per year in the United States alone.

The mood elevators should not be confused with the stimulants, such as amphetamines, caffeine, and cocaine, which act at different sites and produce different effects. Mood elevators have been demonstrated to have significant and lasting effects on endogenous depression—that is, depression that appears to stem from within the patient rather than being a reaction to distressing external events. In fact, when a single therapeutic dose of an antidepressant is administered to a normal individual, the typical result is not elevated mood but drowsiness often sufficient to produce sleep. When normal research subjects receive daily therapeutic doses of tricyclic antidepressants over several weeks, anxiety, unsteadiness, and thinking difficulties are noticed. However, when depressed patients take similar doses, in most cases there is a gradual but significant improvement in mood—usually observable within two to three weeks after the initiation of therapy. In effect, antidepressants pharmacologically distinguish between the normal and the clinically depressed individual.

It is necessary for the prescribing physician to alert patients that they may not experience improvement for a few weeks, because mood elevation is gradual. Uninformed patients may feel even worse when they experience no rapid change after therapy has commenced.

Tolerance to the antidepressant actions of this family of drugs does not appear to develop, even after protracted use. In fact, it is not unusual for patients to take a daily maintenance dose for years. There is some evidence that physical dependence occurs at least occasionally, and a withdrawal syndrome, manifested as nausea, headache, and malaise, has been reported after abrupt termination of use.

Certain common unpleasant side effects occur initially with these drugs, most notably blurred vision and dry mouth; however, tolerance to these effects usually develops with regular use.

Given the prevalence of incapacitating chronic depression in our society, the introduction of the tricyclic antidepressants is of major significance, and their value ranks with that of the phenothiazine major tranquillizers.

Narcotic Analgesics

See the articles in section 3 on the following: codeine, heroin, hydromorphone (Dilaudid), meperidine (e.g., Demerol), methadone, morphine, naloxone (e.g., Narcan), oxycodone (e.g., Percodan), pentazocine (Talwin), and propoxyphene (e.g., Darvon). See section 4 for articles on anileridine (Leritine), diphenoxylate (Lomotil), hydrocodone (e.g., Novahistex DH), levallorphan (Lorfan), and opium.

Drugs classified as narcotic analgesics may be naturally occurring, semisynthetic, or wholly synthetic. The naturally occurring opiates (morphine and codeine) are obtained by refining opium, the crude tarlike exudate cut from the unripe pods of the poppy *Papaver somniferum,* a flowering annual found in many areas of southern Asia and Asia Minor. Among the approximately 20 alkaloids of opium, only morphine and codeine have psychoactive properties; the former comprises about 10%–15% of the opium exudate and the latter, 1%–2%. Semisynthetic narcotic analgesics (also referred to as opiates), such as heroin or hydrocodone, are derived by chemical manipulation of either morphine or codeine. Some of them are considerably more potent than the naturally occurring substances from which they are derived. The synthetic agents (known as opioids), such as methadone or meperidine, mimic the effects of the opiates, but they are not prepared from opium.

The prefix *narco-* in ancient Greek meant to deaden or benumb.[1] All of the narcotic analgesics share the common property of benumbing and thus relieving pain. That is why the name "narcotic" is used for members of this class of drugs, despite substantial structural dissimilarities among them and despite considerable variation in their degree of effectiveness. Further, they produce sedation and, in higher doses, sleep. (Morphine derives its name from the Greek god of sleep, Morpheus.) Still, certain narcotic analgesics are clinically employed specifically for other actions common to the narcotic analgesics, including suppression of the cough reflex and control of diarrhea. Some are also employed in the management of physical dependence on certain other narcotic analgesics. Chronic use of any of the narcotic analgesics at sufficient doses can result in physical and psychological

[1] Although it was also later used in reference to sleep or stupor: e.g., *narcolepsy.*

dependence; unfortunately, at present there is no known alternative which is as effective in ameliorating moderately severe to severe pain without creating significant dependence problems for the user.

HISTORY OF USE

"Opium" is derived from the Greek word *opion*, meaning poppy juice. Opium has been used for its pleasurable (and possibly medicinal) effects for several thousand years. The first known written reference was in a Sumerian text (ca. 4000 B.C.), in which the written representation for the poppy was *hul* ("joy") combined with *gil* ("plant"). The first unequivocal reference to poppy juice was found in the writings of Theophrastus in the 3rd century B.C. Ancient Greek writers were aware of the effects of opium and wrote of the symptoms of habituation and withdrawal. During the Middle Ages, Arab physicians were quite familiar with opium and frequently prescribed it for sedation, relief from pain, and the management of dysentery. It is believed that opium was first introduced to the Orient by Arab traders.

Opium made its way to Europe during the Renaissance and was one of the first drugs to be used in calming manic conditions. It was the great German physician Paracelsus (1493–1541), however, who was credited as the first to compound laudanum—a name initially designating any of the many opium preparations but now restricted exclusively to tincture of opium. Subsequently, during the mid-16th century, within a few decades laudanum became widely used throughout Europe for a variety of physical and mental illnesses.

In 1803, a young German pharmacist, Sertürner, isolated the alkaloid morphine from opium and named it. (Codeine was isolated 30 years later.) Although morphine was in general use as a pain killer in the 1830s, its enormous potential was not realized until after the perfection of the hypodermic needle in 1853 by the Scottish physician Alexander Wood. Its significantly more rapid action and greatly enhanced potency when administered by injection led shortly thereafter to its extensive and invaluable (but often excessive) use among the wounded in the American Civil War and later in the Franco-Prussian War. The practice resulted in the physical dependence of literally tens of thousands of soldiers. In fact, physical dependence on morphine was so widespread among the wounded that it was referred to as "soldier's disease."

In the 1880s cocaine was briefly thought to be effective in treating "morphinism." But as scholars and physicians increasingly reported that cocaine was not only ineffective but also addictive in its own right, its use for this purpose was discontinued. Heroin, first synthesized in 1874, also enjoyed brief, but considerable, popularity with physicians at the end of the 19th century. It was considered to be both a possible analgesic substitute for morphine (possessing three times morphine's analgesic potency) and a possible cure for morphine addiction. However, the harmfulness of heroin was subsequently recognized by the medical profession, as is observed in the following:

> "In reviewing the very remarkable history of the rapid increase in the use of this drug, its wide popularity as a therapeutic agent, the acclaim with which it was received by the medical profession, and the persistence with which manufacturers advertised its virtues, both in technical and lay publications, it is astonishing that physicians were so slow to recognize its dangers and that for six or eight years of its employment there were only a few among the large number who proposed its employment in an ever increasing number of conditions, and who appreciated the harm that was being done . . . ." (Terry & Pellens, 1928).

In the early decades of the 20th century, highly restrictive legislation regarding production, importation, distribution, trafficking, possession, and medical uses of narcotic analgesics was introduced in North America and Europe. This legislation was mainly the result of:

- the alarming failures of the medical profession to comprehend fully the dangers and the widespread abuse of the highly addictive heroin;
- the large numbers of morphine addicts on both continents;[2]
- the easy availability of narcotic analgesics in a variety of preparations, many of which required no prescription; and
- what some observers regarded as growing hysteria in the United States and Canada over continued, uncontrolled use of opium among the ethnic Chinese (in the notorious opium dens), which was viewed as a menance to the "American way of life." (At the same time there were also widespread but ill-founded fears that

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[2] Although their numbers were dwarfed by the enormous population of opium addicts in China, the result of over a century of large-scale opium trafficking by British and to a lesser extent European, American, and Chinese nationals, many of whom amassed huge fortunes.

> wholesale cocaine-induced[3] crimes of violence would be perpetrated by blacks against whites.)

While law enforcement officials continued to be frustrated in their attempts to extinguish the steady flow of illicit opiates into North America and Europe, they did greatly reduce it. However, a serious outgrowth of their efforts was a unique criminal subculture of narcotic analgesic (mainly heroin-using) addicts. Not only was the possession of these drugs now made illegal in many countries, but their reduced availability also led to higher prices, which, for many in turn, could be met only through criminal activities. As well, supporting the habit was an increasingly sophisticated but clandestine chain of "connections": from the producers in Asia and Asia Minor, through a host of go-between buyers, chemists, wholesalers, smugglers, "cutters,"[4] and a pecking order of dealers (many of whom also "cut"), before reaching the street consumer.

Scientists, too, met with frustration as they searched for a cure for morphine and heroin dependence as well as for a potent analgesic alternative without significant dependence-producing properties. Efforts directed toward the development of synthetic products were given a major impetus when, in World War II, Germany was unable to import much-needed morphine. Methadone, which possesses an analgesic potency approximately equivalent to morphine, was synthesized and introduced in wartime Germany. It is usually credited as the first widely used synthetic narcotic analgesic. Meperidine (e.g., Demerol) had been synthesized earlier (1939), but was initially employed only as an antispasmodic agent until its analgesic effects were recognized several years later. However, hopes that these agents and subsequent synthetic narcotics would not produce physical dependence when they were chronically used were not realized. In fact, they became drugs of abuse themselves. However, some of them produce a less severe withdrawal sickness than heroin or morphine when chronic use is abruptly terminated.

PHARMACOLOGICAL ACTIONS

Absorption, Distribution, and Elimination

Morphine and heroin are seldom administered orally, since they are much less potent when taken by this route than when injected. Morphine, when absorbed from the gastrointestinal tract, must first pass through the liver before reaching the rest of the body. A large proportion of the absorbed morphine is broken down by the liver during this "first pass." Because heroin is rapidly transformed into morphine in the stomach, it too suffers the same fate. By contrast, when injected into veins and muscles or under the skin, these drugs initially bypass the liver and are therefore metabolized much more slowly than when taken orally. Therefore, heroin or morphine users will not ordinarily waste their drug by taking it orally.[5]

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[3] While cocaine is legally classified as a narcotic in Canada and the United States, it is pharmacologically classified as a central nervous system stimulant.

[4] "Cutting" is a street term for diluting.

The needle routes also provide the drug with relatively more rapid access to the bloodstream and hence to the brain where the desired effects are initiated. Intravenous administration (injection of the drug directly into the bloodstream) produces the most immediate and intense effects.[6] However, even when intravenously administered, a substantial proportion of the drug substance never reaches the brain, for the reason that narcotic analgesics travel in the bloodstream in protein-bound and water-soluble salt forms which do not readily penetrate the blood-brain barrier. In general, this barrier permits only gradual and incomplete passage of the drug into the brain, thereby restricting the amount which can reach those specific brain target sites where the main actions of narcotic analgesics are initiated. Thus the concentration of narcotic analgesics is found to be much lower in the brain than in such other organs as the lungs, kidney, and liver after the drugs are distributed from the bloodstream throughout the body. Since heroin is much more fat soluble than morphine, it penetrates the blood-brain barrier much more quickly. This difference is believed to account for the higher potency and the more intense "rush" after intravenous administration of heroin.

These drugs are metabolized by the liver before being excreted in the urine.[7] In the case of most narcotic analgesics, metabolism is quite rapid and (with a few exceptions such as methadone) the duration of action is therefore brief—three to five hours.

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[5] The loss of potency of these two drugs when they are taken by mouth can be as much as 90%.

[6] In their pure form all of the narcotic analgesics can be injected; nevertheless, some retain a significant degree of their potency even when taken by mouth, including hydromorphone (e.g., Dilaudid), hydrocodone (e.g., Novahistex DH), and oxycodone (e.g., Percodan). Because oral consumption of these drugs does not present the problems associated with chronic needle administration, they have recently gained popularity among abusers.

Analgesia

The primary pharmacological action for which morphine and many other narcotic drugs are administered is their ability to reduce sensitivity and emotional response to pain. Although some of the commonly used narcotic analgesics are employed for other purposes, all possess this attribute in varying degrees. At the weaker end of the scale are such drugs as codeine and propoxyphene (e.g., Darvon), which are indicated for mild to moderate pain. Such drugs as meperidine (e.g., Demerol) and anileridine (e.g., Leritine) are employed for moderately severe pain. At the most potent end of the scale are morphine and oxymorphone (e.g., Numorphan), which are ordinarily employed only for severe pain.

When considering the analgesic effects produced by narcotics, it is useful to think of two dichotomous components of pain: the sensation of pain, and the affective or emotional reaction to that sensation. In the case of the former, recent research evidence indicates the presence of specific narcotic analgesic receptor sites in cells located in certain ascending pain pathways of the spinal cord and brain. Although the identification of the precise receptor itself and of the mechanism of analgesic action remains to be more fully determined, it is believed that the narcotic drug must bind to these sites in order to produce its analgesic effect. The distribution of the receptors in the central nervous system suggests that they may allow the drug to interfere with the transmission of impulses from pain stimulus receptors before these impulses can reach the higher brain centres responsible for perception and awareness of pain.

Of considerable interest is the high density of the narcotic analgesic receptors in certain areas of a group of subcortical brain structures (i.e., brain structures other than the cerebral cortex), collectively referred to as the limbic system. Although they also play a role in many other functions, certain limbic structures have been demonstrated to be related to the generation of emotional sensations. For example, when particular limbic regions in experimental animals are electrically stimulated, a fright reaction similar to that produced by a painful stimulus is observed. As well, stimulation of other, yet to be fully defined, limbic areas will cause animals to work very hard in order to receive further stimulation. These so-called "pleasure-producing" structures have also been demonstrated to be present in humans. The evidence comes from patients' reports when implanted electrodes are stimulated prior to psychosurgery. While firm conclusions cannot yet be drawn, the emotional components of pain seem to be mitigated, at least in part, by the interaction of narcotic analgesics and the limbic receptor sites.[8] Here may lie the explanation of the suppression of the negative emotional reactions to pain and the concurrent production of the typical euphoria associated with narcotic drugs.

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[7] For example, morphine is inactivated in the liver largely through conversion to its 3-monoglucuronide metabolite, and up to 90% of morphine and its metabolites are then excreted into the urine and the remaining 10% chiefly in the feces.

Effects Other than Analgesia

1. Initial experiences with narcotic analgesics are usually not exclusively euphoria-producing. In fact, some users experience anxiety or depression during their first few drug-taking episodes.[9] Many neophyte users, both medical and nonmedical, suffer from such common side effects as nausea and vomiting. However, in most cases these unpleasant effects either are transitory or disappear with a downward dose adjustment. Thus, an inexperienced heroin user may continue to use the drug in spite of its early effects rather than because of them; often he must await the development of tolerance to them before being fully able to appreciate the desired actions of heroin.

2. Many narcotic analgesics are powerful cough-reflex suppressants (antitussives), and such agents as codeine, hydrocodone, and hydromorphone are widely used in cough-control medications. Hydrocodone and hydromorphone, the more potent with regard to both cough suppression and euphoric action, are popular among street abusers. Both can produce physical dependence (as can codeine at doses greater than prescription levels) when they are chronically abused. For this reason, considerable research effort has been directed toward the development of a satisfactory cough-suppressant drug in this class without physical-dependence-producing (or analgesic) proper-

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[8] Those treated with narcotic analgesics often report that they still perceive the painful stimulus but are no longer bothered by it.

[9] Others may never experience euphoria; many of these are medical patients who nevertheless respond favorably to the analgesic effects of these drugs.

ties. Dextromethorphan (e.g., Robidex), with a cough-suppressant potency approximately equivalent to codeine, has met these criteria. It is now marketed by several pharmaceutical firms in North America. Side effects are reported to be few and very mild.

3. All narcotic analgesics possess strong antidiarrheal properties. Morphine and opium have been invaluable in areas where amoebic dysentery is a major problem, since morphine's ability to produce constipation prevents the development of profound and possibly fatal dehydration. However, the choice of a drug as potent as morphine is limited to only very serious conditions. In lesser conditions, even the mildest of narcotics such as diphenoxylate (Lomotil), which possesses no analgesic action at therapeutic doses, is sufficiently effective in controlling diarrhea.
4. Narcotic analgesics depress the brain centres responsible for breathing before they depress other biological processes such as the functioning of the heart.[10] Death from overdose therefore nearly always results from respiratory arrest. Hence, management of overdose includes artificial support of respiration until the drug is adequately eliminated from the body, or the use of narcotic "antagonist" drugs which promptly reverse the effects of overdose.

Narcotic Agonists and Antagonists

The narcotic analgesics are one group of drugs for which scientists have discovered effective antagonists. These antagonists go to the sites of action in the brain where the drugs (agonists) normally operate, occupying the drug receptor sites and displacing the agonists from these sites. Thus the antagonists in sufficient doses prevent the drugs from producing their effects.

In theoretical considerations of the magnitude of a drug's action, two major characteristics of the drug are considered—its affinity for its receptor and its efficacy. Affinity refers to the ability of the drug to bind to the appropriate site of action (i.e., its receptor), and efficacy refers to the ability of the drug to initiate its effects once it has reached the site of action.

A very active agonist drug is usually considered to have both strong affinity and high efficacy—which is to say, it operates very efficiently. A pure antagonist also has strong affinity for the appropriate site of action, but it has no ability to bring about drug action or effect once it has reached that site. Its role is simply to occupy the receptor, thus blocking the effects of the agonist without producing an effect of its own. There are in addition partial agonists/antagonists, such as levallorphan (e.g., Lorfan), which are compounds with a high degree of affinity but considerably less efficacy than agonists in bringing about the drug effects. Therefore, while they block the effects of the agonist drugs, they produce a weaker effect of their own.

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[10] At very high narcotic analgesic blood levels, however, the heart may stop beating.

Agonists, antagonists, and partial agonists/antagonists have all been used in the treatment of narcotic analgesic dependence. Opiate and opioid drugs act at a finite number of receptor sites in the brain, and the net effect produced at these sites at any time will depend on what proportion of the receptors are occupied by an agonist, an antagonist, or a partial agonist/antagonist. When two or more of these drug types are present, they may be considered to occupy the receptors in a "musical chairs" fashion, with the molecules "sitting down on" and "leaving" the receptors very rapidly in competition with each other. Therefore, the proportion of the receptors occupied by any one of these drug types at any one time will be related to (1) how many drug molecules of that drug type are in the environment of the receptor sites as compared with how many molecules of the other drug types, and (2) the relative efficiency of the various drug types in "sitting down on" the receptor (i.e., the affinity).

If morphine is the only drug administered to a patient, the patient will experience the full effects of the morphine because only morphine molecules will occupy the receptor sites. If increasing amounts of a potent antagonist such as naloxone are then injected, the drug effects of morphine will diminish as the naloxone molecules crowd out the morphine molecules. At some point the morphine effect will become effectively zero even though there are still a few morphine molecules present. If large amounts of morphine were then administered, the characteristic morphine effect would be reestablished.

The use of antagonists entails some risk in drug-dependent persons. If both agonist and antagonist are administered to a person who is not drug-dependent, the antagonist functionally displaces the agonist from its sites of action, and thus returns the person to a normal drug-free state. In contrast, the drug-dependent person's body functions comfortably only when some narcotic molecules are interacting with narcotic receptors; such a person, reduced to an effectively drug-deficient state because of the action of an antagonist, will show withdrawal symptoms appropriate to the degree of physical dependence. This type of response forms the basis for the use of narcotic antagonists in the clinical assessment of the degree of a patient's physical dependence on narcotic drugs. In terms of practical medicine one should never administer morphine without having the antagonist present; nor should one administer an antagonist (e.g., naloxone) without having the agonist (e.g., morphine) present in case there is a sudden need to mitigate the intensity of the patient's reaction to the antagonist.

The narcotic antagonists have also been used in producing special dosage forms of methadone for maintenance/treatment programs. Methadone taken orally has several useful characteristics for such programs: it has a prolonged duration of action; and although in treatment doses it does not produce euphoria in tolerant patients, they are not subject to withdrawal. When naloxone combined with methadone is taken orally, the naloxone is absorbed and then metabolized so rapidly on its "first pass" through the liver that it has no effect on narcotic drug receptors in the brain, while the methadone is less rapidly metabolized and has its desired effect. However, if the combination is administered by injection, both drugs will reach the receptors in the brain, and the naloxone will diminish or eliminate the effects of the methadone. In fact, the amounts of the two drugs are usually calculated so that the naloxone effects will predominate, and the needle user will experience a withdrawal reaction if the combination is injected. Therefore, the presence of the naloxone makes these special dosage forms of methadone unattractive to the illicit market.

MEDICAL USES

In all of the above-noted clinical uses for narcotic analgesics, their function is in symptom management rather than modification of the underlying pathology (i.e., the cause of the pain, diarrhea, cough, etc.).

There are several factors to be considered in the physician's choice of a narcotic analgesic for a specific clinical purpose. These factors include differences in potency, specific side effects, and certain pharmacological properties such as duration of action and dependence liability. As well, consideration must be given to size of dose, route of administration, and necessary period of use/administration. For example:

1. Morphine is both a powerful antitussive and an antidiarrheal agent, but the very high risk of dependence militates against its use in all but very extreme circumstances.
2. Such drugs as meperidine, oxycodone, and methadone retain a substantial degree of their analgesic efficacy when administered orally and are good choices when administration by injection is medically ill-advised. Many others, including morphine, lose much of their potency when taken orally.
3. As well, under some conditions (e.g., in the case of the later stages in the terminally ill patient with severe pain) the relative comfort of the patient is very likely to be of justifiably greater concern to the physician than the dependence liability of a particular drug.

In this last circumstance, there still remains the important issue pertaining to daily dosage. The overly cautious physician may indeed be too concerned about the propensity of a drug to produce dependence and therefore prescribe it in insufficient doses; the result is unnecessary suffering and pain for the patient. On the other hand, the overly "generous" physician who prematurely prescribes unnecessarily large doses creates a different problem. Acquired tolerance to the high dose, after chronic use, may pose a significant dilemma for both patient and physician, for further increases may put the patient prematurely at risk.

Other Issues Pertaining to Pain

Evidence indicates that sharp, localized pain is usually poorly relieved by the narcotic analgesics. By contrast, duller, less well localized, and more chronic pain tends to be controlled very effectively in most cases by these drugs. There appear to be distinct pathways conveying each form of pain to higher perceptual centres, and only in the case of the dull/chronic pain are narcotic receptor sites distributed along its pathway.

While pain resulting from certain tissue inflammation (e.g., arthritis) may be substantially reduced by ASA, narcotic analgesics alone are not effective. For this reason, when moderate to moderately severe pain results partially or largely from inflammation, narcotic combination compounds which take advantage of ASA's anti-inflammatory property have proven to be quite effective (e.g., oxycodone and ASA in Percodan, codeine and ASA in 292).

Because of the danger of physical dependence with chronic administration, it is generally agreed that, unless otherwise clearly indicated, therapy for symptomatic relief from pain should be initiated with non-narcotic analgesics and, when appropriate for the emotional components of pain, non-narcotic sedatives or minor tranquillizers.[11] Avoidance of narcotics is particularly essential with regard to chronic conditions accompanied by mild to moderate pain, such as certain types of headache and back pain, where psychological causes are a distinct possibility. Also, the premature and continued administration of narcotics could very well mask both the underlying pathology and treatment progress in the case of those disorders where pain is a primary symptom. However, it should be stressed that, under the close supervision of a physician, relatively short-term or occasional use of narcotics for relief from moderate to severe pain does not ordinarily produce physical dependence and can be justified in the case of recurring conditions.

Methadone Maintenance and Withdrawal

Until the mid-1960s, North American society's basic response to heroin-dependent people was to incarcerate them and compel them to undergo total withdrawal ("cold turkey") followed by abstinence; sometimes this approach was supported by adjunctive psychotherapeutic, social service, and/or institutional care. Generally, despite the most humane and concerned treatment, the rate of rapid relapse continued to be extremely high, and complete recovery was the exception rather than the rule. However, some therapeutic communities such as Synanon and Daytop Village, which rely on "cold turkey" withdrawal with prolonged post-withdrawal residence, have reported a high success rate among long-term residents, although early dropout rates are also high.

Largely due to the heroin addict's pleasure-seeking basis for commencing drug use and the highly deviant lifestyle, the prevailing popular view was (and to a large extent still is) that the addict is a moral degenerate. This view has traditionally been coupled with a legal posture involving harsh penalties geared toward removal of the abuser from society; little attention has been directed toward developing treatment programs with any reasonable prospects for rehabilitation. Indeed, many observers have even suggested that the "cold turkey" method constitutes additional punishment, and that incarceration does not constitute therapy.

[11] The same applies to the choice of a non-narcotic cough medication and an antidiarrheal preparation.

Given that this traditional legal and medical approach was clearly ineffective, the New York City Health Council in 1963 granted funds to Dole and Nyswander to develop a methadone maintenance pilot project for heroin addicts. Among available choices, methadone possessed several advantages over most other narcotic analgesics:

1. Because of the high potency of methadone, cross-dependence between it and other powerful narcotic analgesics such as heroin and morphine occurs. That is to say, when substituted in sufficient quantities methadone can fully block withdrawal sickness which would otherwise naturally occur in physically dependent users after abrupt abstinence.
2. When administered orally, methadone retains much of its efficacy in reducing "drug hunger" without renewing euphoria.
3. Because of its long duration of action, only a single daily administration is required.
4. Cross-tolerance between methadone and other narcotic analgesics also occurs. Therefore, patients maintained on large daily oral doses of methadone will not experience the euphoric or other desired effects of heroin (or other narcotic analgesic) even when it is intravenously injected. Since the desired effects no longer occur, narcotic-injecting behavior may soon be extinguished in the regular methadone user.
5. Chronic maintenance on therapeutic doses of methadone does not appear to produce serious health problems.

The maximum oral dose, taken daily usually in a fruit juice mixture at a legally designated methadone-dispensing unit, is approximately 120 mg; however, most patients are stabilized at doses of 50 to 80 mg per day. For a significant minority, the results of methadone maintenance have been a less deviant and criminal lifestyle and, with the assistance of rehabilitation services, a greatly increased probability of productivity and self-sufficiency. Although methadone maintenance is not a cure for narcotic analgesic dependence, nevertheless, after almost two decades, it has been demonstrated to reduce significantly the rate of relapse to illicit drug use.

An alternative treatment model to indefinite methadone maintenance is methadone withdrawal, a program involving substitution of methadone for the illicit narcotic analgesic and the gradual reduction of the daily dose of methadone usually over a period of several weeks or months until a drug-free state has been achieved. Although this approach to withdrawal produces moderately unpleasant symptoms, they are not nearly so severe as those of "cold turkey." However, critics have pointed out that while gradual withdrawal is more humane, there is little evidence that complete detoxication in this manner is in the long run more effective than the "cold turkey" method.

Proponents of methadone maintenance point to the humaneness of this approach to the physically dependent person; they can also correctly point to research evidence indicating that many methadone-maintained patients, when provided with rehabilitative assistance, are able to lead productive lives. However, the following points must also be considered:

1. Methadone can produce profound physical dependence which can result in a lengthy and painful withdrawal if the drug has been used at high daily doses and is then abruptly terminated.
2. The first-year dropout rate for many methadone maintenance programs is reported to be quite high—often up to 50% or even higher; many dropouts reportedly return to illicit drug abuse.
3. Many patients have been known to abuse drugs other than narcotic analgesics while participating in methadone maintenance programs. The other drugs most often recorded in these instances are stimulants such as amphetamines and cocaine, cannabis, and sedative/hypotics such as barbiturates and alcohol.

The British Narcotic Analgesic Addict

Prior to 1961, the number of known narcotic analgesic addicts in Great Britain was less than 500. These were mainly middle- and upper-middle-class persons, most of whom were also middle-aged. All were believed to be iatrogenically addicted (i.e., as an inadvertent result of medical treatment). They were maintained usually on morphine by their personal physicians, who were encouraged but not required to report them to the Home Office. In the early 1960s, the number of heroin addicts increased at an alarming rate. These newer addicts differed from the known chronic group in that they were substantially younger, were mainly drawn from the lower social classes, and often had a history of criminal behavior. By 1968 there were almost 3,000 narcotic analgesic addicts known to the Home Office. Several theories were offered in attempting to account for this almost sixfold increase in such a brief span of time. Two possibilities, however, seem to account best for the phenomenon: excessive prescribing practices of a few London practitioners whose addict patients either sold or gave away their excess supply; and the increasing willingness of young people to engage in socially deviant drug-using behavior during the 1960s.

In 1968 legislation was passed requiring the addict to register with the government in order to obtain heroin or other narcotic analgesics exclusively for addiction maintenance at designated clinics and only from specially licensed physicians. Although the number of newly registered addicts declined during the early 1970s, it is believed that the tighter restrictions over the medical dispensing of heroin have resulted in greater demand for it (at much higher prices) on the black market. The scope of the problem in Great Britain has never reached that encountered in the United States.[12]

ABUSE OF NARCOTIC ANALGESICS

The euphoria produced by narcotic analgesics is not only a key component in overall relief from pain but also the primary reason for their abuse. Indeed, the greater the euphorogenic potential of a given narcotic analgesic, the more likely it is to be prized by abusers. Generally, those narcotics which possess the greatest analgesic potency (heroin and morphine) also tend to produce the greatest euphoria, although this is not always the case. The extent of the relationship between euphoria and analgesia among these many drugs requires further investigation.

Several factors influence the degree of euphoria experienced by users of narcotic analgesics. In addition to the properties of the particular drug, the most significant of these factors are:

- size of dose administered;
- route of administration;
- innate and acquired tolerance of the user to narcotic analgesics (see below: Tolerance and Dependence); and
- whether or not the drug is taken in combination with other drugs.

Size of Dose

Among the narcotic analgesics, intensity of euphoria is dose-related, smaller doses being required in the case of the more potent drugs. Many weaker drugs in larger quantities can produce a degree of euphoria comparable to smaller doses of the more powerful substances. However, in the case of many of the commonly used weaker drugs, high doses can produce serious adverse effects; for example, with both codeine and propoxyphene very high doses can produce seizures.[13]

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[12] In Canada, the prevalence of narcotic analgesic abuse is also much lower than that in the United States.

Route of Administration

As noted earlier, administration by injection is superior to oral administration because the effects are experienced more rapidly and because the intensity of euphoria is much greater as less of the drug is wasted. Intravenous injection ("mainlining") is the preferred method. It is only via intravenous injection that the user can achieve a "rush," an immediate intense orgasmic sensation in the abdomen; however, not all heroin users experience this phenomenon. Although most often associated with intravenous administration of heroin and morphine, even propoxyphene can produce such a "rush" when taken intravenously.[14] Because the highly pleasurable "rush" occurs so rapidly after injection, the two events become associated. Eventually, in the chronic user, the act of injection itself tends to produce powerful secondary gratification—that is to say, the very act of injecting a substance even when it is not psychoactive can become highly rewarding.

Advantages of Oral Administration

All of the narcotic analgesics lose some of their euphoric potency when orally ingested. Nonetheless, legally produced potent narcotic analgesics intended for oral administration[15] have several advantages for the street user:

1. The quality (purity) of street drugs such as heroin is variable and generally poor; by contrast, there is very high consistency of quality in the narcotic analgesics produced by the legitimate pharmaceutical industry.
2. Because these narcotic analgesics are formulated so as to retain sufficient potency when taken orally, they can provide a level of

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[13] Regular narcotic analgesic abusers tend to resort to these weaker drugs only when their preferred drug is not available.

[14] The occurrence of a rush is not exclusive to narcotic analgesics, Intravenous users of methamphetamine and cocaine report a similar phenomenon.

[15] E.g., oxycodone, hydromorphone, hydrocodone, meperidine.

euphoria and tranquility acceptable to many regular street users.

3. Most licit oral preparations of narcotic analgesics are available at local pharmacies; an abuser can obtain them by theft, by forged prescription, or often by legitimately written prescription.[16]
4. By taking oral preparations a user avoids the discomforts and health hazards associated with chronic needle administration and nonsterile equipment.
5. If the user obtains the drugs from a pharmacy (by whatever means), the risk of being "burned" (cheated) on the street is avoided. The likely result of being "burned" is the onset of withdrawal sickness.
6. The user is not at the mercy of either the often extreme fluctuations in the price of street heroin or, even worse, the periodic complete "drying up" of street sources.

Combination Drug Abuse

The overwhelming majority of street heroin addicts acknowledge experience with several other drugs of abuse. Many who have tried a combined "hit" (intravenous injection) of heroin and cocaine or methamphetamine claim that it produces an even greater "rush" than when each is administered alone. However, only occasionally is the North American street-drug user able to purchase any of these drugs in a relatively undiluted state. Thus, administering a potent "speedball" (heroin plus either stimulant) is more a fantasy than reality for the average user, whose combination "hit" in all probability produces a milder initial effect than would a moderately potent dose of street heroin (10%–20% pure).

Addiction in the Medical Profession

Another significant group of narcotic analgesic abusers comprises some members of the medical profession and other workers in hospital settings. Surveys taken during the past few decades have indicated that their abuse of and dependence on narcotics is greater than for the general population. Some observers have noted that the availability of such drugs in hospitals and medical clinics is the most important consideration in attempting to account for the disturbing rate of this illicit use. Still, while the percentage is higher for these professionals than for the general population, only a small fraction are reported to be abusers. The clear suggestion is that, as with the general population, personality factors are of crucial importance in precipitating abuse.

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[16] Many abusers are highly adept at faking the appropriate medical symptoms and complaints.

Possible misconceptions about narcotic analgesics, even among physicians, also likely play an important role in abuse. Significantly, although morphine is also available, meperidine (e.g., Demerol) is the most frequently cited narcotic analgesic of abuse. The lesser potency of meperidine may give rise to some mistaken beliefs:

- that it possesses a very much lower addictive potential than morphine;
- that the probability of physical dependence on orally administered narcotics (frequently the route of administration for meperidine) is quite low; and
- that the "habit," even after protracted use, would not be difficult to break because meperidine is so widely and safely used with patients.

None of these beliefs is valid.

EFFECTS OF NARCOTIC ANALGESIC ABUSE

The following factors must be considered when evaluating the possible effects of narcotic analgesics on the abuser:

- the pharmacological actions of this class of drugs;
- the tendency toward chronic injection of the drugs; and
- the deviant lifestyle.

Drug Effects and "Needle" Effects

Most narcotic analgesics do not produce serious adverse consequences with chronic use (the major exception being the creation of physical dependence). Those symptoms which do generally occur include constipation, pupillary constriction (which results in impaired night vision), blurred vision, reduced libido, menstrual irregularity, and mood instability. The last is due mainly to the relatively short period of action of most narcotic analgesics. It should be noted, however, that there is an increased probability of respiratory impairment, which may in turn facilitate the development of serious pulmonary complications.[17] Chronic high-dose abuse of a few narcotic analgesics, such as meperidine and propoxyphene, differs from abuse of most other narcotic analgesics in that these drugs may also cause such adverse CNS-stimulant effects as persistent muscle twitches and tremors, hyperactive reflexes, startle responses, agitation, and occasionally seizures and/or toxic psychosis.

Harmful effects directly related to actual chronic needle administration include abscesses, other local irritation and infections at the sites of administration, collapsed veins, and such potentially serious diseases as viral hepatitis and tetanus resulting from the use of nonsterile equipment.

Lifestyle

Heroin and other narcotic analgesics are available to the dependent street user only through illicit means or by deception of a physician in the case of drugs available by prescription.[18] Further, because procuring the necessary funds to buy the drugs (or procuring the drugs themselves) often involves theft, prostitution, and other illegal activities, regular criminal behavior is closely linked to the dependent user's day-to-day life. Crimes of violence are not unusual within the drug subculture; however, unlike with "speed" (methamphetamine) and cocaine, violent behavior does not directly result from the pharmacological effects of the narcotic analgesics.

The life of the street user may be described as characterized by a sense of urgency, heightened by constant attempts to avoid withdrawal sickness. For needle users, obtaining funds for a buy is only part of their daily concern. As noted earlier, those who purchase their drugs mainly on the street are presented with a number of risks (e.g., being "burned," or faced with a dramatic escalation in cost or the complete drying up of street supplies).[19] As well, for all addicts, there is the constant fear of arrest.

Many addicts have cogently observed that they ultimately want only one source of security—a continuous supply of their drugs. In desperate times the drugs may be stolen from even the closest of personal friends. In other words, in the face of withdrawal sickness, drug-seeking behavior is usually egocentric, and at that time the needs of others are often of diminished importance to most addicts. Social relations are therefore typically erratic and to a significant extent dictated by drug availability.

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[17] The incidence of both pneumonia and tuberculosis is significantly higher among narcotic addicts than the general population.

[18] Some low-potency codeine combination products are available in Canada without prescription.

[19] The last two are most likely to occur after a large quantity of drugs has been confiscated by the authorities. Addicts point to this as a "panic" situation.

Researchers consistently report that addicts of all ages (particularly needle users of heroin) have significantly higher rates of generally poor health, serious illness, and mortality than their contemporaries in the general population. In addition to the health problems already discussed, the following variables also contribute:

1. Street addicts spend most of their money maintaining the habit, leaving little for adequate nutrition, housing, or medical care.
2. Needle users are afraid that their drug habit will be easily detected because of the "trackmarks" clearly visible on their arms and other parts of the body. For this reason they likely will avoid medical attention until illness becomes quite serious.[20] Moreover, lung disorders and venereal disease attain a particularly high incidence in this group, conditions for which early diagnosis and treatment are essential. The high incidence of complications in pregnancy among dependent women is related to inadequate prenatal care.
3. Addicts rapidly acquire tolerance to the euphoric effect of the weak heroin available on the streets. They therefore often resort to other drugs (which also can produce dependence) in order to achieve a pleasurable "high"; however, multiple drug abuse can have serious results. Because narcotic analgesic users ordinarily do not suffer any serious adverse effects directly resulting from the actions of these drugs, they often make the mistake of tacitly assuming they can continue to take large quantities of other drugs with the same degree of safety. Many deaths among heroin addicts have been attributed to overdose

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[20] By contrast, the oral abuser may see as many as a dozen physicians per week, complaining, for example, that a "chronic cough" is not adequately relieved by weaker preparations.

of drugs other than heroin, such as barbiturates and similar sedative/hypnotic drugs.[21]

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance develops to the euphoric, analgesic, sedative, respiratory-depressant, and emetic (nausea-producing) effects of narcotic analgesics, but not to their pupillary and only slightly to their constipating actions. (Chronic users must regularly use laxatives.) The result may be, in the course of the long term, that a tenfold or greater daily-dose increase is needed to produce the desired intensity of effect. To put it another way, there is a tenfold or greater decrease in the sensitivity of the body to the effects of the drug.

Death from Overdose: Unlike with barbiturates and other sedative/hypnotic drugs, substantial tolerance to respiratory-depressant effects does occur with narcotic analgesics. However, most deaths resulting from narcotic analgesic overdose, even among heavy regular users, are due to respiratory arrest. Many experts believe that sudden death in dependent users (particularly of heroin) following intravenous injection is usually due to a much greater purity of drug than that to which they are accustomed—that is, instead of the generally low purity of ordinary street heroin, the purity of the dose that proves lethal is substantially higher and the respiratory-depressant effects are beyond the user's tolerance. However, sudden death may also result from other respiratory or cardiovascular complications.

Tolerance to Pleasurable Effects: To compensate for acquired tolerance to the subjectively pleasurable effects of narcotic analgesics, users periodically increase their daily dose. After chronic use, they can reach a dose plateau beyond which no amount of narcotic analgesics can produce the desired intensity of effects.[22] However, drug-taking continues daily at the plateau dose level, in spite of the loss of pleasurable effects;

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[21] However, the most common cause of death among heroin addicts is, in fact, from heroin or other narcotic analgesic overdose: see Tolerance and Dependence.

[22] This pattern assumes that users are able to obtain sufficient amounts of their drug to increase the dose at will. For most street heroin addicts this is unlikely; for them, their maximum daily dose is ordinarily restricted by the lack of availability of heroin and by its high cost.

but now the drug is taken primarily to avoid withdrawal. Desired levels of sensitivity can be restored only after withdrawal and at least several weeks of abstinence.

Cross-Tolerance: Once users become tolerant to any given effect produced by one narcotic analgesic at a given daily dose, they will also be tolerant to that same effect of all other narcotic analgesics at comparable doses. This phenomenon is known as cross-tolerance. For example, 10 mg of morphine provides the same analgesic effect as 100 mg of meperidine when both are administered by subcutaneous injection. A user who has acquired tolerance to the analgesic effect of the 10 mg of morphine will also be tolerant to the analgesic effect produced by 100 mg of meperidine.

Dependence

Physical Dependence: Chronic use or abuse of narcotic analgesic drugs can produce physical dependence, and abrupt abstinence from them can result in withdrawal sickness. The kinds of symptoms, as well as their severity and duration, are affected by: (1) the particular drug, (2) the chronicity and pattern of use, (3) the typical daily dose, (4) the concurrent use of other drugs, (5) the general health status of the user, and (6) the chosen route of administration (oral vs. needle).

Contrary to popular belief, narcotic analgesic withdrawal (unlike sedative/hypnotic withdrawal) is rarely a life-threatening medical problem in otherwise healthy adults. In fact, although withdrawal can cause considerable suffering, several of the main symptoms resemble those of a moderately severe bout of influenza.[23] It is quite unusual for symptoms to include the seizures which often accompany sedative/hypnotic withdrawal. Additionally, in the case of street heroin, in many areas of North America the drug is so highly diluted that the dependent user is likely to experience relatively mild withdrawal symptoms, compared to users in other parts of the world whose heroin is substantially more pure.

The peak intensity of withdrawal symptoms commonly occurs in a physically dependent user between 48 and 72 hours after the last administration. However, early withdrawal symptoms may begin within a few hours; for example, morphine users often experience withdrawal symptoms within six hours or less after the last drug administration. It is therefore not surprising to find users taking drugs three, four, or five times a day, with each administration being preceded by some degree of early withdrawal discomfort. Since methadone is excreted more slowly than other narcotic analgesics, withdrawal symptoms appear and reach a peak later in methadone users.

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[23] It should be kept in mind that North Americans usually experience rather mild forms of influenza.

Psychological Dependence: The issue of duration of withdrawal reactions is in dispute; some evidence suggests that withdrawal reactions can persist six months to a year after the last drug-use episode. However, there is a very real problem in distinguishing between psychologically based abstinence signs and biologically based abstinence signs, and this problem complicates assessment of the duration of withdrawal reactions. There is clear evidence in the case of amphetamine-like drugs that sleep disturbances last for several months following termination of drug use; while the narcotic analgesics case is not nearly so clear, the possibility of prolonged physical withdrawal should not be dismissed in favor of an explanation entirely in terms of psychological factors.[24]

Cross-Dependence: Some drugs when administered can suppress the withdrawal symptoms produced by abstinence from another drug of the same class. This phenomenon is known as cross-dependence, and it has been demonstrated to occur generally among narcotic analgesics. For example, as noted earlier, methadone is a highly potent drug capable of suppressing even heroin withdrawal (if administered in sufficient quantities). The less potent narcotic analgesics, such as codeine and propoxyphene, also can suppress withdrawal resulting from abrupt abstinence from more powerful narcotic analgesics; however, they may have to be administered at doses sufficiently great to cause potentially serious side effects.

Neonatal Drug Dependence

When a mother is physically dependent on narcotic analgesics during pregnancy, at birth her child experiences an abrupt termination of the drug supply via the mother's circulation and will experience a withdrawal reaction that can be life-threatening if not treated. The reaction is characterized by excessive restlessness, irritability, highpitched crying, tremors, gooseflesh, runny nose, and various other withdrawal symptoms similar to those shown by adults. It is not known whether the period of fetal dependence has any predisposing effect on later drug-seeking behavior. It appears that methadone users impose more severe withdrawal reactions on their offspring than heroin or morphine users, although there is some argument on the point.[25] In the case of the two latter drugs, symptoms of the withdrawal reaction are usually noticeable within a few hours; with methadone the onset is usually slightly later because of its longer duration of action. Some of the symptoms may persist for weeks or even months after birth.

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[24] Symptoms which may last for protracted periods of time after the classical phase of narcotic analgesic withdrawal is completed can include depression, anxiety (sometimes with periods of severe agitation), insomnia, loss of appetite, and a persistent craving for narcotic analgesics.

REFERENCE

Terry, C.E., and Pellens, M., *The Opium Problem*, For the Committee on Drug Addictions in Collaboration with the Bureau of Social Hygiene, Inc., New York, 1928.

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[25] Nevertheless, because mothers in methadone programs tend to receive better prenatal care, babies exposed to methadone *in utero* are generally larger and healthier than heroin-exposed babies, and therefore have a better prognosis, despite the more severe withdrawal symptoms.

Stimulants

See the articles in section 3 on the following: amphetamines, caffeine, cocaine, diethylpropion (e.g., Tenuate), methylphenidate (e.g., Ritalin), and nicotine. See section 4 for articles on ephedrine, fenfluramine (e.g., Pondimin), phenmetrazine (e.g., Preludin), phentermine (e.g., Ionamin), and strychnine. See notes on aminophylline and khat in section 5.

The class of drugs known as stimulants contains widely disparate groups of substances with few properties in common other than their ability to increase activity in the central and autonomic nervous sytems. Many common substances have stimulant properties: for example, the nicotine in cigarettes and the caffeine in coffee, tea, and cola beverages.

There are certain medical problems for which the stimulant effects of drugs are desired—for example, narcolepsy, a rare but serious sickness characterized by sudden inappropriate (in terms of time, place, or need) and uncontrollable attacks of deep sleep. In many instances, however, other stimulant properties are therapeutically undesirable and can detract from the management of medical problems for which one of these drugs is used. For example, the anti-asthma drug aminophylline is useful because it opens up the bronchial tubes and eases breathing; on the other hand, these same stimulant effects at other sites can increase heart rate and in some cases cause nervousness and sleeplessness.

Although the stimulant effect of this class of drugs may be sometimes undesirable from a medical point of view, the mood-altering effects of certain stimulants are highly sought after by many illicit users. Those stimulants which cause the gravest public health problems because of their high abuse potential are cocaine and the amphetamines as well as the newer amphetamine-like drugs.[1]

[1] It should be noted that some drugs which are structurally related to amphetamines (e.g., MDA and PMA) are usually classified as hallucinogens rather than stimulants; yet these drugs also have significant stimulant properties. See the chapter on Hallucinogens above.

HISTORY OF USE

Cocaine

Cocaine, a stimulant obtained from the leaves of the South American coca bush, *Erythroxylon coca*, is known to have been used by Indians in South America for at least the past 1,200 years, according to archeological estimates of the age of graves containing coca leaves and of pottery with coca-leaf emblems. In its most primitive use, the coca leaf is chewed. Cocaine, the chief active principle (and about 1% of the weight), is absorbed through the mucous membranes of the mouth.

During the pre-Inca era, chewing of coca leaves is thought to have been widespread among native Indians in the Andes of Peru, Bolivia, and northern Chile. At the height of the Inca era, coca-leaf chewing was forbidden to all but the aristocracy and priesthood, although there is evidence that Inca physicians may have employed cocaine's local-anesthetic properties for trephining (circular perforation and removal of bone tissue from the skull). By the time of the arrival of the Spanish conquistadors in the early 16th century, however, the practice of coca-leaf chewing had again become widespread. That cocaine increases endurance, depresses appetite, and produces a general state of euphoria in its users were realities of considerable significance to Indian workers, who were required to perform hard work at high altitudes and withstand inadequate diet. The Spanish disdained the practice of coca-leaf chewing, and initially attempted to eradicate it. However, they quickly learned that enslaved Indians were both more able and more willing to perform heavy labor if payment was in the form of coca leaves. To this day, many Andean Indians continue to chew coca leaves.

Coca plants were brought to Europe before the end of the 16th century, but there was little interest until the biochemist Alfred Neiman isolated the pure cocaine substance in the early 1860s. Within 20 years of his discovery, cocaine had come to enjoy widespread use as a local anesthetic and, less scientifically, as a component of countless patent medicines, confections, lozenges, and beverages designed to treat any number of minor and often imagined afflictions. In the early stages of modern medical use, cocaine was thought to be an effective treatment for morphine addiction. Sigmund Freud strongly advocated such use until a close friend, a fellow physician whom he was treating, became one of the first recorded cocaine addicts and cases of cocaine-induced psychosis. Robert Louis Stevenson was treated with cocaine for tuberculosis in 1885. It was at this time he is believed to have sketched the first draft of his classic *Dr. Jekyll and Mr. Hyde.* Shortly thereafter, in North America, Coca-Cola containing cocaine was introduced and marketed not only as a pleasant-tasting beverage but also for relief of fatigue and headache.

Despite the number of prominent people who extolled the virtues of cocaine, evidence on both sides of the Atlantic regarding its very high addiction potential and its ability to induce bizarre behavior had grown so rapidly that by the beginning of the 20th century its sanctioned uses were drastically curtailed. In 1903, for example, it was completely discontinued as a constituent in Coca-Cola. Three years later the United States Pure Food and Drug Act specifically forbade the interstate shipment of all food or soft drinks containing cocaine and also restricted the importation of coca leaves.

With increasing legal constraints, cocaine rapidly disappeared as a significant drug of abuse in North America and Europe. Its medical use for such maladies as depression, alcoholism, and gastrointestinal disorders was also increasingly restricted. However, because of its important local-anesthetic properties, it still retains some limited medical use, mainly to induce surface anesthesia on the mucous membrane of the nose and throat. For other purposes, other new local anesthetics have been synthesized which, while possessing the anesthetic properties, lack psychoactive effects.

During the 1960s, cocaine made a substantial comeback, particularly among heroin addicts desiring its euphoric effects. Additionally, the drug gained popularity among musicians, sports figures, entertainers, artists, and certain groups of intellectuals. But because the cost has remained prohibitively high (some estimates suggest a street price of well over $100 per gram), cocaine is viewed as the Rolls Royce of drugs of abuse, restricted primarily to the affluent and to some criminal segments of society. Its stimulating actions, along with its ability to produce a remarkable state of euphoria, assure that cocaine is likely to continue to be a prized nonmedical drug.

Amphetamines

The amphetamines and amphetamine-like drugs are relatively new synthetic compounds. The prototype, amphetamine, is structurally related to the naturally occurring stimulants ephedrine and adrenaline. It was first synthesized in 1887, although its medical uses were not recognized until much later. In 1927, it was discovered that amphetamine raises blood pressure, constricts blood vessels (thus giving rise to effects such as increased blood pressure and nasal decongestion), and dilates the small bronchial air sacs. As a consequence of this last finding, amphetamine was marketed as a bronchodilator in the early 1930s under the trade name Benzedrine. Also at about this time, physicians began to use the drug for its effect as a central nervous system stimulant. Amphetamine was used in its early years as a mixture of two chemical forms, dextroamphetamine and laevoamphetamine (i.e., d- and l-amphetamine). When these two components of the original drug were separated and studied individually, it was found that dextroamphetamine (later marketed as Dexedrine) was much more active than laevoamphetamine as a CNS stimulant. This separation of the two forms of amphetamine was the first of many chemical refinements aimed at finding a central stimulant with minimal undesirable peripheral side effects such as increased heart rate and rise in blood pressure.

By this time the medical importance of this group of drugs was generally acknowledged, and their stimulant properties were already being used in treatment of a number of medical conditions. As early as 1935, physicians were using amphetamine to combat narcolepsy. In 1937, amphetamine was discovered to be useful in combating hyperkinesis in children, a disorder characterized by excessive restlessness and hyperactivity.

During World War II, amphetamines gained widespread popularity particularly among pilots, who exploited them for their endurance-increasing properties. Later, many others who sought these same effects—truck drivers, athletes, students, etc.—made their use commonplace.

By the mid-1940s, amphetamines were prescribed for two additional reasons, to combat depression and to suppress appetite in obese patients. However, availability for these purposes has now been largely curtailed by legal restrictions.

Early enthusiasm for and endorsements of amphetamines by both medical practitioners and researchers gradually diminished during the late 1940s as evidence mounted that abuse of amphetamines had reached alarming proportions. In the United States, the abuse of Benzedrine for its powerful euphoric and stimulant properties was so widespread that in 1949 its manufacturer, Smith Kline & French, responding to social and legal pressure, replaced it with a new product, Benzedrex, which contained a weaker stimulant, propylhexedrine. (Up to this point, the more powerful Benzedrine had required no prescription.) In postwar Japan, the first of many epidemics of amphetamine abuse among young people was recorded. Through the early 1970s similar drug crises were to occur in Great Britain, Australia, the United States, and Europe. Additionally, an enormous number of nondeviant adults, particularly women in the United States, were regularly consuming amphetamines prescribed for weight management. The demand was so great during the 1960s and early 1970s among both abusers and legitimate medical users, that in the United States alone several billion amphetamine tablets were produced every year, with the peak at approximately 12 billion in 1971.

Although certain significant physical and psychological health hazards of the use and abuse of amphetamines were examined in medical papers as early as the 1930s, the extremely harmful effects of these drugs were most dramatically brought to light in the late 1960s after young abusers discovered that the euphoric effects of amphetamines, particularly methamphetamine ("speed"), were greatly enhanced with administration by injection. Had there been any lingering questions regarding the potentially damaging effects of the abuse of amphetamines, they were rapidly answered by the introduction of "speed." Its users are characterized not only by their numerous serious medical, social, psychiatric, and legal problems, but also by a lifestyle very similar in many respects to that of heroin addicts. Indeed, some researchers believe that those dependent on "speed" have a prognosis for recovery as poor as heroin addicts, and that their cost to society is equally great.

Although initially the major source of street amphetamines had been supplies illegally diverted from the legitimate pharmaceutical industry, more stringent controls over their production and distribution resulted in a significant reduction of legally produced amphetamines and a corresponding proliferation of illicit supplies from "basement" laboratories set up mainly to produce "speed." Survey evidence based on police seizures and street-drug analyses, as well as reports from long-term users, indicated a consistent decline in the quality (purity) of available "speed" during the 1970s. The result, according to many observers, has been a parallel reduction in its use. However, to conclude that there has been an overall decline in street stimulant abuse may be erroneous. Several less potent amphetamine-related drugs (discussed below in more detail) such as phenmetrazine, methylphenidate, diethylpropion, and phentermine have more recently gained considerable favor among stimulant abusers.

A decrease has also been evident in the medically sanctioned uses of amphetamines, which are now limited to the treatment of only a few disorders. Many of the earlier medical uses were later found to be (1) of little or no benefit (as in the treatment of functional psychosis and opiate addiction), or (2) of questionable or uncertain benefit (as in the treatment of psychic depression), or (3) of only short-term benefit (as in the treatment of obesity).

The prescribing of amphetamines for weight reduction was largely discontinued as a result of the belated recognition by many physicians that, while amphetamines temporarily suppressed appetite and reduced hunger pains, tolerance to their effects often rapidly developed in many patients, necessitating increased daily doses in order to maintain the desired appetite-suppressant action. Chiefly because of their stimulant and euphoric properties, many patients acquired dependence on them and refused to discontinue their use even when their therapeutic value had been exhausted. In response to the problems presented by amphetamines, the pharmaceutical industry developed a plethora of chemically related "diet pills" to replace them. However, none has been demonstrated successfully to retain long-term appetite-suppressant effects, and many, when chronically used, can also produce in addition to tolerance a significant dependence. Indeed, the high abuse potential and dependence liability of certain amphetamine-like substitutes has resulted in either the complete discontinuance of their marketing in Canada, as with phenmetrazine (Preludin), or reclassification of legal status to the level of a controlled drug under Canada's Food and Drugs Act, as with diethylpropion (Tenuate) and phentermine (Ionamin).[2]

Comparison of Cocaine and the Amphetamines

From a biochemical perspective, cocaine and the amphetamines have different mechanisms of action. Nevertheless, because the overall impact of their mechanisms is the same, we have some explanation as to why cocaine and the amphetamines parallel each other so closely in their basic clinical symptoms and in the behavioral problems that arise from their use. Indeed, so far as the initial euphoric effects upon intravenous administration are concerned, experienced users are unable to discriminate between them (although a distinction is perceptible within a few minutes, for cocaine's effects dissipate much more rapidly than those of the amphetamines).

[2] Methylphenidate is now also a controlled drug in Canada. Like amphetamines and unlike diethylpropion, it cannot be prescribed for weight reduction.

Cocaine differs significantly from amphetamines in one important regard. In addition to its stimulant properties, cocaine has local-anesthetic properties which may be associated with respiratory depression and convulsions at high dose levels. Amphetamines can also produce convulsions, but these are of a different origin and are much less likely to occur. Hence, cocaine is more likely to produce lethal consequences associated with overdose-induced respiratory depression or convulsive states, although the death rate from these causes is quite low.

PHARMACOLOGICAL ACTIONS

In low to moderate doses, most drugs which stimulate the CNS can cause heightened feelings of well-being, and at high enough blood levels many such drugs produce intense euphoria. However, these effects are not universal. In fact, at some point in the drug-taking episode, most people will experience mild anxiety, tension, nervousness, or even agitation whether or not they experience the desired effects. Stimulants may also increase wakefulness and mask the signs of fatigue, prolonging the user's ability to perform work requiring endurance or normal levels of concentration. Nevertheless, stimulants can produce insomnia and can interfere with normal sleep, effects which can be quite harmful with chronic abuse. As well, stimulants tend to suppress appetite and reduce hunger pangs. In most instances, however, the above effects tend to last for short periods of time and may be greatly reduced after a few weeks of regular use as tolerance develops.

Among the more significant autonomic nervous system effects which many stimulants exert on the body, and which are generally regarded as unfavorable side effects, are increased heart rate and blood pressure, constriction of the blood vessels, dilation of the pupils, and increased rate of respiration—symptoms often described collectively as the alarm reaction. While most stimulants are likely to produce an increased state of arousal, this is not invariably the case. For example, the appetite suppressants fenfluramine (e.g., Pondimin) and chlorphentermine (e.g., Pre-Sate) can (surprisingly) produce drowsiness and sedation, although the side effects more typically associated with other related stimulants may also occur.[3]

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[3] For other effects of stimulants at low to moderate doses see the articles noted at the beginning of this chapter on the specific stimulant substances.

MEDICAL USES OF AMPHETAMINES[4] AND COCAINE

In Canada, amphetamine (Benzedrine) and dextroamphetamine (Dexedrine) are mainly prescribed for hyperkinesis in certain children and for narcolepsy. Less frequently, their other legitimate clinical uses include the management of certain types of epilepsy, the counteracting of the CNS-depressant effects of barbiturates prescribed for epileptics, the management of the symptoms of parkinsonism, and the management of hypotensive (low blood pressure) states associated with anesthesia. They cannot be prescribed in Canada for transient or chronic depression, to combat fatigue, to enhance alertness, for obesity, or for their nasal-decongestant properties. For this last purpose, they have been replaced by propylhexedrine, ephedrine, and other weaker stimulants.

Cocaine no longer has any recognized medical uses except (now very infrequent) as a local anesthetic in nose and throat surgery.

Depression

Both cocaine and amphetamines have recently been studied to determine their potential as psychotherapeutic agents in the treatment of hospitalized clinically depressed patients. Superficially, it may appear reasonable that drugs which stimulate both physiologically and psychologically and also induce euphoria should produce favorable effects in depressed persons. Indeed, in the past, such was the reasoning of many physicians who prescribed these drugs to treat chronic states such as general malaise and depression resulting from feelings of inadequacy. However, both cocaine and amphetamines proved to be largely ineffective for these uses. In the case of more seriously depressed patients, some are reported to have responded with elevated mood but only for brief periods. Cocaine was not effective in any cases when orally administered, and even in those patients who did respond to injected administrations with favorable mood changes (e.g., calmness or euphoria), the dysphoric components of their illness were usually not eliminated. That no long-term studies have been performed suggests that further controlled investigation should not be ruled out. However, based on current information, the effects of these drugs on chronic depression are far less predictable than those of the widely used antidepressant drugs, such as amitriptyline (e.g., Elavil), which have a number of advantages.[5] The latter often improve mood without ex-

[4] And amphetamine-like drugs.

[5] See the article on the Tricyclic Antidepressants in section 3.

cessive stimulation; they have a very low, almost nonexistent, dependence liability; and they tend to improve appetite and sleep rather than interfering with them as most CNS stimulants do. By contrast, cocaine and amphetamines have been known to result in behavioral arousal and increased mental activity without concomitant elevation of mood, sometimes with the result that the patient gains sufficient energy to attempt suicide.

Appetite

To varying degrees, stimulants which affect the central nervous system have an anorectic effect—that is, they suppress appetite. However, the physiological mechanisms which produce that effect are not fully understood. While lower brain centres, such as the hypothalamus, are known to exert direct effects on appetite in laboratory animals, other factors must be considered in humans. For example, some human studies have shown that weight loss associated with amphetamines could be just as much attributed to increased activity and feelings of well-being as to actual suppression of appetite. Further, standard medical references remind the physician that patients taking drugs indicated for weight management tend to lose only a fraction of a pound more per week than dieters not receiving drugs. Whichever may be the case, it appears that those using amphetamines and the newer substitute drugs may well be faced with significantly greater problems than advantages. Although the user may lose weight, the fact remains that the effect of amphetamines on weight and on appetite suppression is transient. Studies to date have shown that when users stop taking appetite suppressants, they experience a rebound hunger, so that whatever weight was lost tends to be regained. The occurrence of ravenous eating after amphetamine use is stopped has been proposed as evidence that amphetamines produce a state of physical dependency; by contrast, when people eat after a period of starvation due simply to food deprivation, they tend to eat not ravenously but moderately.

Extensive clinical research has provided a basis for the consensus that amphetamine use in the treatment of obesity is not sufficiently beneficial to justify the risk of dependence and other complications. Therefore, a decision was taken to transfer the amphetamines to the controlled drug classification of Canada's Food and Drugs Act (Schedule G) and to restrict the purposes for which they could be prescribed. It is therefore likely that their widespread use in Canada for the treatment of obesity is at an end. However, in spite of their very questionable benefit, many newer amphetamine-like appetite suppressants remain available by prescription, all to some extent sharing many of the amphetamines' disadvantages.

Hyperkinesis

A number of children experience a nervous disorder known as hyperkinesis, characterized by abnormally high levels of usually dysfunctional and nondirected activity, impulsiveness, distractability, and low frustration tolerance. These children have great difficulty fitting into the structured environment of school and tend to perform very poorly in all structured settings. Difficulties in coping with their child's excessive activity can also produce marked stress in the parents' relationship with the child. Conflicts with parents and with structured environments often burden the child further with emotional problems and inordinately low feelings of self-esteem.

When such children are given tranquillizers—which one might think would be the appropriate medication to calm them—they paradoxically show increased rather than decreased activity. However, amphetamines, amphetamine analogues (such as methylphenidate), and caffeine have been shown to produce beneficial effects in many hyperkinetic children, paradoxically not further stimulating them but rather inducing decreased activity, more controlled and directed behavior, decreased impulsiveness, and increased attention span. Furthermore, although the reasons are not understood,[6] hyperkinetic children do not appear to develop tolerance to these effects; nor do they acquire physical dependence on the stimulants employed. Current evidence involving follow-up studies of adult addiction patterns in formerly hyperactive children suggests that heightened vulnerability to drug dependence does not take place. One reason may be that the development of tolerance and dependence usually results from taking stimulant drugs in order to go from a normal state to a hyper state. In the case of hyperkinetic children, however, the change is from a state of hyperactivity toward normalcy, and the effect of producing normalcy does not appear to have the attendant or later consequence of producing dependence.

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[6] One widely accepted proposal views hyperkinetic children as having minimal brain dysfunction (MBD), a condition in which there is a biochemical imbalance in the brain so that the brain does not control behavior in the usual way. In this model the stimulants are used to partly correct these biochemical disturbances.

Another theory suggests that in the hyperkinetic child, the brain's cortex (containing the higher centres of brain function) does not receive a sufficient number of stimuli from the environment when the child is involved in a normal amount of activity, and that the child's abnormally high level of activity is an adaptive mechanism to increase the stimuli reaching the cortex so that it may function normally. In terms of this theory, amphetamines are considered to increase the number of stimuli reaching the cortex at normal activity levels, so that the compensatory excessive activity is no longer required.

Stimulant therapy is not effective in all hyperkinetic children. Even when it is effective, certain adverse effects, most commonly anorexia and insomnia, are evident. Some researchers believe that the lower-than-average growth rate of some hyperkinetic children may be due to inadequate nourishment resulting from anorexia during their formative years.

The fact that stimulants do not invariably prove useful in the management of hyperkinesis may be due to differing etiologies in those children collectively diagnosed as hyperkinetic. (It has been estimated that close to 5% of all children may be hyperkinetic.)

THE ABUSE OF STIMULANTS

Although cocaine in the form of coca leaves has been in use among South American Indians for more than a thousand years, it is unlikely to have been greatly abused: tradition-directed societies do not tolerate aberrant behavior and mete out severe punishment to rule-breakers. Stimulant abuse appears to be a relatively recent phenomenon, beginning for cocaine when it was isolated in the late 19th century and for amphetamines only a few decades ago. In the case of each, in spite of early "cries in the wilderness," its harmfulness was widely recognized only after abuse had reached epidemic proportions. Now researchers agree that these drugs possess a very high dependence liability, and that their attractiveness clearly results from the exhilaration, intense euphoria, and increased energy which, at sufficiently high doses, they produce in the user.[7]

Stimulant Psychosis

Chronic abuse of very high doses of amphetamines (especially methamphetamine by injection) and cocaine can result in serious psychological consequences, ranging from chronic agitation and anxiety states to toxic psychosis. The latter resembles acute paranoid schizophrenia in many respects. As early as 1940, one scholar pointed to the dangers of methamphetamine use and the close parallel between the psychological reaction to it and to cocaine; he noted as well the resemblance between the effects of chronic use of amphetamines and the classical cocaine psychosis, which had been described several decades before. The psychosis produced by stimulants appears to be related to the level of the drug in the blood and not necessarily to any inherent predisposition or weakness in the user; in other words, given a high enough dose, even psychologically normal individuals would experience a psychotic reaction. In fact, amphetamine-induced psychosis has been shown to be associated with very specific blood drug levels. Hence, the physician's first line of attack is to lower that level. Recovery can be hastened by administering urinary acidifying agents and/or diuretics, which facilitate rapid excretion of the amphetamines in the urine.

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[7] Laboratory animals, for example, will work harder and longer for a reward of cocaine than for any other drug of abuse.

Stimulant psychosis is characterized at first by increases in suspiciousness and paranoid thinking, progressing to full-blown paranoid delusions, typically of persecution. The person may perceive even close friends and relatives as a danger and may react with unprovoked hostility and (sometimes bizarre) violent behavior. Both suicides and homicides have been committed in a state of stimulant psychosis. Early on, pseudohallucinations occur (i.e., hallucinations known to be unreal by the person experiencing them). The most common are of an auditory and visual nature, and they are typically followed by true hallucinations (i.e., hallucinations believed to be real). Although auditory and visual hallucinations are more common, tactile and olfactory hallucinations also frequently occur. Tactile hallucinations, such as the feeling that bugs are crawling over one's body or under one's skin, are similar to those experienced by alcoholics undergoing withdrawal. Further, the person characteristically engages in seemingly meaningless behavior which is compulsively repeated for extended intervals.

Although the point is somewhat overlooked in the literature, stimulant psychosis and schizophrenia do differ in certain respects. The predominant hallucinatory experience in stimulant-induced psychosis is visual, whereas auditory hallucinations occur significantly more frequently in schizophrenics. Furthermore, tactile and olfactory hallucinations common to stimulant psychosis are unusual in any of the major schizophrenic disorders. Unlike many schizophrenic patients, stimulant-induced psychotics often fully retain memory, clear consciousness, and orientation with regard to time, place, and self. Assaultiveness and violence are not common events among schizophrenics, folklore to the contrary notwithstanding. In contrast, the rate of violence among stimulant-induced psychotics is high. Most significant, however, is the fact that after the stimulants have been excreted, the toxic psychosis readily disappears in the large majority of cases.[8]

High-dose abuse of the following amphetamine-like drugs has produced psychotic symptoms virtually identical to those produced by cocaine and the amphetamines: chlorphentermine (e.g., Pre-Sate), diethylpropion (e.g., Tenuate), fenfluramine (e.g., Pondimin), methylphenidate (e.g., Ritalin), phendimetrazine (e.g., Plegine—no longer marketed in Canada), phenmetrazine (e.g., Preludin—no longer marketed in Canada), and phentermine (e.g., Ionamin).

"Speed" (Injectable Methamphetamine)

When injected intravenously, "speed" (and cocaine) produce powerful sensations referred to as a "rush," which many users feel cannot be adequately described in words. Some have suggested that it is akin to an intense orgasm. Many of those who have experienced the intense euphoria associated with intravenous injection of "speed" become regular "mainliners," prizing "speed" over all other drugs. Nonetheless, the overwhelming majority of "speeders" do report regular use of many other drugs, sometimes in combination with methamphetamine.

The use of "speed" began in the mid-1960s in San Francisco and other large American cities, and within a few years it had gained wide popularity, particularly among young people in the 18–25 age bracket. At that time "speed" was relatively easily available on the streets, often diverted from the legitimate pharmaceutical industry and usually of fairly high quality. However, a rapidly growing body of reports concerning methamphetamine-related health and social problems led authorities to order a sharp curtailment of production and tighter controls over distribution.[9] Among these problems were "speed"-related violence and other criminal behavior, the appearance in emergency departments of users suffering amphetamine psychosis, and the high rate of disease and other health problems secondary to methamphetamine injection (e.g., viral hepatitis due to nonsterile needles) and lifestyle problems such as poor nutrition and inadequate housing.

[8] Latent psychotics whose disorder was precipitated by stimulants may not recover for quite some time.

[9] In Canada the drug is no longer legally produced.

In spite of the serious health problems, there is little evidence that injected methamphetamine contributes directly in a significant way to lethality. In other words, "speed kills" is an overdramatization of its hazardous effects. Indeed, reported deaths resulting specifically from either the pharmacological actions of methamphetamine or related to secondary complications arising from its injection have been very infrequent. But the catchiness of the phrase led to the erroneous notion that amphetamines were particularly lethal in comparison to other street drugs. Even in cases of acute overdose or chronic administration in very high doses, the death rate is slight when compared to that of many other drugs of abuse. Part of the reason may be that in the case of other drugs associated with a high death rate from overdose—particularly the CNS depressants (e.g., narcotic analgesics, barbiturates, and other sedative/hypnotics)—death is generally caused by their respiratory-depressant effect. By contrast, amphetamines stimulate breathing.

However, death from overdose of any of the amphetamines (including "speed") has occasionally resulted from cerebrovascular hemorrhage, acute cardiac failure, or extremely high fever. In addition, deaths have resulted from secondary complications, such as viral hepatitis contracted from nonsterile needles.

Probably the largest number of deaths which may be viewed as "speed"-related result from the psychological effects of the drug—that is, the paranoid thinking and violent behavior so frequently observed. There have been several documented reports of homicides, lethal accidents, suicides, and self-mutilations by "speed" users. Case reports suggest that more than a few may have been suffering from psychosis at the time of these events. Although evidence of a connection may not be present, it is probable that "speed" has been involved in many other violent deaths among street drug users.

Other Harmful Effects

Withdrawal from amphetamines after chronic high-dose use tends to result in psychic depression, sometimes so severe as to provoke suicide.

Deaths resulting directly from either accidental or deliberate overdose of amphetamine-like drugs or cocaine are quite infrequent. However, with any of these drugs tissue inflammation and damage occurs at the sites of injection when they are injected on a regular basis. Cocaine, when regularly sniffed, inflicts substantial damage to nasal and sinus tissue.

Simultaneous Use of Other Drugs

One of the more frequently observed phenomena among those who chronically use amphetamines and amphetamine-like drugs is a state of overstimulation, agitation, insomnia, and anorexia. Users often resort to cannabis, narcotic analgesics, or sedative/hypnotics in order to combat these adverse effects, as well as for these drugs' own euphorogenic properties. In fact, CNS-depressant drugs (including alcohol) are so frequently and widely consumed by amphetamine-dependent users that multidrug dependence is quite common.

On the other hand, many heroin addicts seek amphetamines and/or cocaine for their euphoric properties, particularly when they are no longer able to achieve euphoric effects from heroin. They do, however, continue to regularly administer heroin in order to avoid the discomfort of withdrawal. Neither amphetamines nor cocaine can suppress the withdrawal sickness resulting from abrupt abstinence from heroin or other narcotic analgesics or from barbiturates or other sedative/hypnotics.

TOLERANCE AND DEPENDENCE

Issues Resulting from Medical Uses

One of the main features of amphetamine and related drugs is that tolerance to many of their principal effects develops rapidly with regular use. Fortunately, however, in the case of two of the three primary clinical uses of these drugs—in the treatment of hyperkinesis and of narcolepsy—neither tolerance to the desired effect nor dependence on the drug appears to develop even with protracted use.

By contrast, tolerance to the appetite-suppressant effect can develop even at therapeutic doses within a few weeks. This is a significant liability of their use in the treatment of obesity. In order to maintain (not necessarily intensify) the desired levels of appetite and hunger-pain suppression, the user may require consistently increasing doses, which also heighten the probability and/or intensity of unwanted side effects (e.g., anxiety, overstimulation, and insomnia). Some users may come to desire the other effects of the drugs: euphoria, greater alertness, and increased energy. Tolerance to these can also quickly develop with regular use. To compensate, patients have been known to increase their daily dose unilaterally, often obtaining prescriptions from more than one doctor. Users may become so highly obsessed with both the effects of the drug and the problems of ensuring its continued supply that it takes on a compelling role in their daily life—that is, they have become psychologically dependent on the drug.

Amphetamine, methamphetamine, phenmetrazine, and phendimetrazine may no longer be prescribed in Canada for treatment of obesity because of their high potential for producing powerful dependence and subsequent abuse. Additionally, they offer no special advantages over the less powerful appetite suppressants. Still, with chronic use, all of the currently prescribed anorexiants are capable of producing tolerance and psychological dependence problems.

It is uncertain whether physical dependence on currently prescribed appetite suppressants can occur if they are chronically administered at no more than the therapeutic daily dose level. As noted earlier, the consistent occurrence of ravenous eating upon abrupt termination of use is believed by some researchers to be sufficient evidence that a state of physical dependence has been produced. However, certain other symptoms of appetite-suppressant withdrawal, such as extreme fatigue and emotional depression, characteristically occur only at daily doses substantially higher than the therapeutic range. The evidence suggests that this issue has not yet been satisfactorily resolved. It is more clear that if psychologically dependent users continue to increase their daily dose, physical dependence is likely.

Issues Resulting from Nonmedical Use

When amphetamines and related drugs are specifically and regularly abused for their euphorogenic and endurance-producing effects, tolerance develops rapidly. The user is therefore frequently obliged to increase the daily dose, possibly to as great as 10 to 20 times the recommended therapeutic range—even greater under certain conditions. Increasing dosage is particularly necessary for the "speed" user.

A fairly regular event in which "speeders" engage is referred to as a "run"; it involves repeated injections over a period of several days without sleep and usually without food. Invariably, "speeders" report that the first "hit" (injection) produces the greatest euphoria, and successive "hits," provided the dose is not increased, produce a declining degree of intensity in the desired effects. Indeed, euphoria gradually gives way to anxiety, then to agitation, and thence to progressively increasing paranoia; ultimately, marked amphetamine psychosis may occur. During this condensed non-stop period of administration, it is evident that tolerance develops extremely rapidly; after such a brief passage of time as 24 hours it is frequently no longer possible to achieve the desired pleasurable response no matter how much of the drug is administered. The "run" usually terminates when the methamphetamine supply has run out or the user is too exhausted to continue. A characteristic withdrawal syndrome, referred to as a "crash," ensues. It is characterized by extended but disturbed sleep accompanied by long periods of REM (rapid eye movement) activity,[10] voracious appetite upon awakening, followed by irritability, lassitude, and moderate to very severe mood depression. After several days of abstinence the syndrome usually disappears and "pre-run" sensitivity to amphetamines is restored. The agitation produced by a "run" may be so great that the user may attempt deliberately to bring on withdrawal (the "crash") through the use of CNS depressants, such as sedative/hypnotic drugs.

Essentially the same sequence of events occurs with abusers of orally administered amphetamine. However, their pattern of consumption (in most cases lower daily doses and more widely spaced administrations) results in considerably more gradual development of tolerance and dependence and in more gradual development of profound psychological impairment. Nevertheless, the long-term effects can be just as severe.

The Special Case of Cocaine

There appears to be considerable disagreement among researchers as to whether or not tolerance and physical dependence result from regular cocaine use. However, there is universal agreement that cocaine produces powerful psychological dependence.

Evidence indicates that, unlike with amphetamines, the daily use of cocaine does not appear to create tolerance to its desired effects. That is, regular use does not require increasingly greater doses in order to produce a consistent euphoric effect from one day to the next.

On the other hand, recent in-depth investigation of a number of cocaine users suggests a parallel between cocaine "sprees" and methamphetamine "runs" with regard to tolerance. ("Sprees" usually are of a shorter duration than "runs.") As with "speed" users, some cocaine users who inject the drug report the need for increasing doses during the course of a "spree" in order to maintain the same potent effects produced by the initial "hit." And for some intranasal users ("snorters") of cocaine there is a substantial loss of effect within 10 to 12 hours. The latter users cite this as a primary reason for terminating the "spree."

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[10] Most dream activity occurs during REM periods.

Some researchers have referred to the phenomenon as "temporary tolerance," which completely disappears as quickly as overnight.

Abrupt termination of regular high-dose cocaine use clearly does not result in dramatic withdrawal sickness, as would be the case with heroin or barbiturates. It has been argued by some that abstinence from cocaine does not usually produce even the relatively moderate symptoms observed after amphetamine abstinence. Nevertheless, mild symptoms qualitatively similar to amphetamine withdrawal sickness, although less pronounced—e.g., exhaustion, depression, lengthy sleep, increased hunger—have been reported with sufficient frequency to suggest that physical dependence on cocaine is possible.

Section 3

Individual Drugs

Introduction

The drugs in this section will be described under the following headings:[1]

Synopsis

A brief overview of the particular drug, including key pharmacological effects, tolerance and dependence, and patterns of use and abuse.

Drug Source

How the drug is produced.

Trade Names

Popular commercial names. Listings are generally not exhaustive. A substantial list of trade names is found in section 6. Trade names are capitalized; nonproprietary names are not.

Street Names

Common slang names applied mainly by nonmedical users.

Combination Products

Examples of two types of combination products are identified here: (1) important legitimate pharmaceutical preparations containing the drug under discussion in combination with one or more other drugs, and (2) common drug combinations taken by nonmedical users and known almost exclusively through street drug abuse.

Medical Uses

Listed here are only those major legitimate uses for which a drug is employed by physicians. In some cases, there may be other less common uses.

Physical Appearance

Generally, only the characteristics of the pure drug are identified. The form and identifying characteristics of legitimate pharmaceutical products (size, color, etc.) are described in standard physicians' references such as the *Compendium of Pharmaceuticals and Specialties* in Canada and the *Physicians' Desk Reference* in the United States. The physical appearance of drugs sold on the street is too often deceptive for a description to be reliable.

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[1] For further discussion of most of these headings, see Understanding Drug Use (section 1).

Dosage

Information about two distinct types of dosage is presented here: (1) the accepted single dose range appropriate for the treatment of certain recognized medical conditions, and (2) the typical single dose range taken by nonmedical users. It should be noted that the figures provided refer to most situations; under certain conditions, more or less of the drug may be taken at any one time.

Routes of Administration

Common methods for taking the drug (e.g., injection, oral) are listed here, including those employed for medical and nonmedical use.

Effects of Short-Term Use: Low Doses

Lower doses taken by nontolerant users are defined in two ways: (1) in the case of a drug which has a common medical use, an amount taken on a specific occasion within the therapeutic dose range; (2) in the case of a drug which is used mainly or exclusively in nonmedical situations, an amount taken on a specific occasion which is typical (i.e., common) for nontolerant users. *At such dose levels, most users are unlikely to experience serious toxic effects.* Nevertheless, it should be kept in mind that, for a number of drugs, there can be a wide disparity with regard to what constitutes a lower dose.

In the context of effects, *short-term* (as opposed to *long-term*) means the same as *acute* (in the medical sense) and refers to the effects produced as a result of a single drug-taking episode.

Effects refers to reactions to a drug. Included here are those which range in incidence between occasionally occurring and frequently occurring. Generally, effects which occur very infrequently are not identified. Effects are divided into several subgroupings:

- central nervous system (CNS), behavioral, subjective;
- cardiovascular;
- respiratory;

- gastrointestinal; and
- other.

Note: In this book drug effects appear in one subgrouping or another according to *manifestation of action* rather than *mechanism of action.* (The latter would refer rather to the underlying cause.) Thus, for example, "rapid heart rate," a common side effect of many drugs, is consistently listed under "cardiovascular" even though the underlying causes of drug-induced "rapid heart rate" can vary.

Effects of Short-Term Use: Moderate Doses

In a few cases, it is desirable to separate the effects of moderate doses of a drug from those of lower doses for the sake of clearer understanding. This approach is logical with certain medically used drugs that are prescribed at different dose levels to achieve different ends. Barbiturates, for example, are usually prescribed at lower doses to produce sedation and at moderate doses to induce sleep.

Effects of Short-Term Use: Higher Doses

Higher doses taken by nontolerant users are variously defined: (1) in the case of a drug which has a common medical use, an amount taken on a specific occasion in excess of the therapeutic dose range for that drug; (2) in the case of a drug which is used mainly or exclusively in nonmedical situations, an amount taken on a specific occasion which is in excess of that typical for nontolerant users. *At such dose levels, the probability of experiencing serious toxic effects is substantially greater than with low to moderate doses.*

Effects of Long-Term Use

Long-term refers to regular (or chronic) use. *Effects* pertains to persistent reactions to the *long-term use* of a particular drug.

Lethality

The propensity of a drug to produce fatal effects.

Tolerance and Dependence

The propensity of a drug to produce tolerance, as well as physical and psychological dependence, with regular use.

Patterns of Use

The incidence and prevalence of use, including prescribing practices and nonmedical use.

Abuse Potential

The degree to which a given drug is abused, or is likely to be abused, in our society, based on an interaction of its dependence liability, inherent harmfulness, and availability.

Amphetamines

DRUG CLASS: CNS STIMULANTS

SYNOPSIS

The amphetamines are a group of central nervous system (CNS) stimulants the most important of which are the original drug amphetamine and its close chemical congeners, dextroamphetamine and methamphetamine.[1] These drugs produce a number of transitory effects the most important of which are wakefulness, alertness, increased availability of energy, reduced hunger, and an overall subjective feeling of well-being.

Amphetamine was first introduced in the 1930s to combat nasal congestion. Subsequently, all three drugs were found to be effective in combating other pathological conditions, including hyperkinesis (hyperactivity) in children and narcolepsy (uncontrollable sleeping episodes). They were also prescribed to control obesity and disorders involving depression; however, it has since been discovered that they are of limited value in treating either condition. Any therapeutic advantage they may have for these two purposes is short-lived and more than offset by the serious liabilities of chronic use: all can produce tolerance to desired effects, physical and psychological dependence, sleep disorders, psychological disturbances, and unwanted appetite suppression for those taking them for other reasons.

At high dose levels, these drugs can create toxic psychosis characterized by paranoid delusions, hallucinations, and, frequently, aggressive or even violent behavior.

The amphetamines have long been abused for their euphoric and stimulant effects. Truck drivers, students, and athletes were among the groups that abused them extensively when they were easily available in Canada because of their abilities to extend considerably the normal periods of wakefulness and endurance. Among street drug users,

[1] Throughout this article "amphetamines" refers to these three drugs.

"speed" (injectable methamphetamine) is the most popular of this group of drugs because of its greater potency and more rapid onset of effects.

Abuse of amphetamines has declined dramatically during the past decade from the near epidemic between 1950 and 1970 in North America and elsewhere. Two key factors have accounted for this:

- severe restriction of medical use through legislation and therefore a concomitant decline in legal production by the pharmaceutical industry; and
- more intense police action against illicit production and traffic, resulting in a decline in quality and quantity of available street amphetamines.

However, although abuse of amphetamines per se has declined, there has been a corresponding increase of interest in and abuse of other stimulants such as cocaine and amphetamine-like substances.

DRUG SOURCE

Amphetamines are produced through chemical synthesis by the pharmaceutical industry and by illicit laboratories.

The drastic reduction in the level of manufacture of legally produced amphetamines has led to a sharp reduction in their diversion for illegal distribution. Most street amphetamines are synthesized in "basement" laboratories.

TRADE NAMES

- amphetamine—Benzedrine;
- dextroamphetamine—Dexedrine;
- methamphetamine—Desoxyn (not available in Canada).

STREET NAMES

Bennies, black beauties, copilots, crystal, dexies, eye openers, lid poppers, meth, pep pills, speed, uppers, wake-ups.

"Speed" usually refers to injectable methamphetamine.

COMBINATION PRODUCTS

Dexamyl is the trade name for a combination of dextroamphetamine and amobarbital.

Street combinations include "goofballs" (amphetamines and barbiturates) and "speedballs" (methamphetamine or cocaine and heroin). While LSD or PCP (phencyclidine) is sometimes combined with the amphetamines, usually the buyer is not aware of the presence of the additional drugs.

MEDICAL USES

Amphetamines have been used to treat:

- narcolepsy (uncontrolled episodes of sleep);
- hyperkinesis (hyperactivity) in children;
- certain types of epilepsy;
- parkinsonism;
- abnormally low blood pressure associated with anesthesia;
- obesity due to improper diet (in Canada, no longer legally prescribed for this use);
- psychic depression (in Canada, no longer legally prescribed for this use).

PHYSICAL APPEARANCE

Legal preparations of amphetamine and dextroamphetamine are white, odorless crystalline powders with a bitter taste, soluble in water and slightly soluble in alcohol. Legal methamphetamine (not available in Canada) also appears as a white, odorless, bitter crystalline powder freely soluble in water and in alcohol.

Illicit preparations include fine to coarse powders, crystals, and "chunks," off-white to yellow in color, supplied loose (in plastic or foil bags) or in capsules or tablets of various sizes and colors (sometimes imitating commercially produced compounds).

Illicitly produced amphetamines often have a strong odor, resulting from incomplete clearing of reagents and/or solvents used in manufacture. The smell may be "fishy," ammonia-like, or otherwise strong and unpleasant.

DOSAGE

Medical

- for narcolepsy—amphetamine or dextroamphetamine in a daily dose range 20–60 mg;
- for hyperkinetic behavior disorders in children—amphetamine or dextroamphetamine in a daily dose range 2.5–40 mg;
- for other indications—e.g., parkinsonism, epilepsy, hypotensive states associated with anesthesia—the physician determines dosage after assessment of condition.

Nonmedical

Dosage for occasional users may be within the therapeutic range (up to 60 mg per day). However, dependent heavy users are likely to take daily doses several times greater. A common cyclical pattern for heavy users consists of several consecutive days of repeated high doses administered intravenously (referred to as a "run") followed by several days of abstinence, interspersed with lengthier periods of less extreme daily doses.

It is difficult to assess the doses used by those relying on illegal sources of supply. Drug users usually exaggerate the amount they have taken. Moreover, the gross weight of amphetamines purchased on the street is often substantially composed of various diluents or impurities. Also, street drug sellers or "pushers" often misrepresent, either knowingly or unknowingly, the substances they are selling; thus amphetamines bought on the street may actually be wholly or in part one of the weaker stimulants such as ephedrine or caffeine or, less frequently, a drug from another class which has stimulant properties, such as phencyclidine (PCP).

Given the above cautions, a reasonable estimate of daily dose for heavy users ranges from 250 to 300 mg per day, although up to 1,000 to 1,500 mg per day has been reliably reported. During a "run," daily doses may be even higher.

ROUTES OF ADMINISTRATION

Most commonly, orally or by intravenous injection, the latter being the preferred method of the chronic, high-dose abuser. Amphetamines are commonly sniffed by occasional or new users. Impurities in street amphetamines may cause irritation of nasal tissue.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, subjective, behavioral: overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, mild confusion, tremor, and, in rare instances, panic and/or psychotic episodes; reduction of appetite; increased alertness and energy, reduction of fatigue and drowsiness, general increase in psychomotor activity, and a heightened sense of well-being.

Cardiovascular: palpitations, increased heart rate, irregular heartbeat, headache.

Respiratory: increased and irregular breathing rate.

Gastrointestinal: dryness of the mouth, unpleasant taste, diarrhea; appetite suppression (which in treatment of conditions other than obesity may be an unwanted effect); retraction of the gum tissues.

Other: increase or decrease in libido, possible temporary impotence; increased urine output.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

Intensification of the low-dose effects may occur as well as any of the following effects:

CNS, subjective, behavioral: intense exhilaration and euphoria, rapid flow of ideas, feelings of increased physical strength and mental capacity, garrulousness; excitation, agitation, and sometimes panic or in some cases depression and irritability; paranoid thinking, confusion, and perceptual distortions including hallucinations; assaultive behavior has also been observed. The amphetamine "rush," an effect greatly desired by the abuser, is a

[2] Single doses within the therapeutic range, up to 60 mg per day in nontolerant individuals.

[3] Above the medically recommended level in nontolerant users, or lower doses in particularly sensitive individuals.

highly pleasurable sensation experienced almost immediately after intravenous injection and felt to be similar to an intense orgasm or to electric shock.

Cardiovascular: excessive sweating, anginal pain, fever, fainting, and cardiovascular collapse.

At very high doses (severe overdose), high fever, convulsions, coma, cerebral hemorrhage, and death may occur.

METHAMPHETAMINE "RUN"

Many methamphetamine abusers, in an attempt to maintain the initial effects of exhilaration and highly enhanced self-confidence, repeatedly inject themselves with the drug several times a day over a period of several days; this is known as a methamphetamine "run." During the first day of the run, feelings of euphoria and elevated self-esteem and intense sexual arousal are commonly reported. Thought patterns tend to be rapid and of a decisive nature. Periods of garrulousness may alternate with periods of intense preoccupation with one's thoughts and behavior. Usually by the second day, the euphoria is gradually replaced by increasing agitation. Thoughts can race so rapidly that concentration becomes extremely difficult. Frightening visual images which are known by the user to be unreal (pseudohallucinations) often occur under these conditions and cannot be controlled. Although less common, true hallucinations (hallucinations believed by the user to be real) may also occur and may be visual, auditory, tactile, or olfactory. Runs usually last between three and five days, or longer, and are usually terminated after the drug supply has run out or the user is too exhausted to continue.

AMPHETAMINE PSYCHOSIS

In addition to true hallucinations, psychotic symptoms, including paranoid delusions, often emerge and may intensify during the course of a run. Uncontrolled and violent behavior may therefore occur. Frequently, seemingly meaningless and bizarre behavior may also be compulsively repeated. In many respects, this toxic state, referred to as amphetamine psychosis, closely resembles paranoid schizophrenia. However, the two states differ in that during amphetamine psychosis the consciousness remains clear and accurate orientation in regard to time, place, and self (identity) is maintained. Memory for events during the episode is also hyperacute. Moreover, paranoid schizophrenics rarely experience tactile hallucinations (e.g., the sensation of bugs crawling on the skin); nor are they likely to experience olfactory hallucinations (e.g., smelling gas when it isn't present). Further, while visual hallucinations such as terrifying visions are the most common in the case of drug-induced psychosis, their occurrence is substantially less frequent in paranoid schizophrenics, who are more likely to experience auditory hallucinations (e.g., hearing a threatening voice).

The psychosis usually disappears after the drug has been metabolized and eliminated from the body.

EFFECTS OF LONG-TERM USE

Regular use at low doses or higher doses can directly produce:

- chronic sleeping problems including insomnia, frequent nocturnal awakening, and poor-quality sleep;
- anxiety and tension states;
- appetite suppression, which may result in disorders related to nutritional deficiency;
- high blood pressure and rapid and irregular heartbeat; and
- skin rash.

In addition, regular high-dose use can also directly produce suspiciousness and paranoid thinking, severe agitation, and in some cases chronic amphetamine psychosis.

In order to combat these drug-related effects, chronic abusers often take cannabis, alcohol, and other sedative/hypnotics and, when available, opiates. The probability of multiple drug dependence among chronic abusers is therefore quite great.

MEDICALLY INITIATED AMPHETAMINE ABUSE

In the past, many patients with no previous history of drug abuse or psychiatric disorder often began abusing amphetamines inadvertently as a result of having them prescribed by their physician. The highly pleasurable response produced by the drug, combined with increasing tolerance to its effects, often led many patients to demand greater amounts. Their physician's failure to comply often resulted in "doctor shopping" with the patient going from one physician to another to collect a number of prescriptions and then getting them filled at different pharmacies. Now, however, such inadvertent development of addiction is much more rare, at least in Canada, since physicians no longer prescribe these drugs for obesity or depression. Within the past decade, restrictions on the prescribing of amphetamines have led many addicted persons to switch to other drugs that are similar in CNS-stimulant effects and are still more easily available by prescription. Some of these alternative drugs, such as methylphenidate (e.g., Ritalin) and diethylpropion (e.g., Tenuate), are now also subject to greater control in response to recent widespread abuse.

"SPEEDERS": ABUSERS OF INJECTABLE METHAMPHETAMINE

"Speeders" generally arrive at chronic use of injectable methamphetamine either through mild to heavy oral abuse of one of the amphetamines or through an established needle habit involving other addictive drugs. For the oral user, graduation to needle use may result from peer pressure, experimentation, increased tolerance to large oral doses, or the desire to achieve the more rapid and intense "high" that administration by injection produces. Occasionally, those addicted accidentally through medical use of amphetamines may graduate to "speeding."

Once regular "speeding" has begun, most users acknowledge that a return to the milder oral route is very unlikely. The needle habit can be so pronounced in some users that merely injecting themselves with water or any other nonpsychoactive substance can be quite pleasurable.

Chronic use of injectable methamphetamine often generates paranoid thinking, exacerbated by, but not by any means chiefly due to, the natural fear of being arrested. The "speeder's" paranoia often extends to close friends, relatives, and even well-known co-users of amphetamines.[4] Along with paranoid thinking, "speeders" also suffer from both lowered frustration tolerance and decreased emotional control, which can culminate in abusive, violent, and occasionally homicidal behavior. Furthermore, the deviant lifestyle of "speeders" in North America increases their vulnerability to the violence of others within the drug subculture.

A frequently serious problem among high-dose users of methamphetamine is severe psychic depression which results after abrupt termination of use; this depression may be so pronounced that suicidal thinking and occasionally suicide attempts may result.

INDIRECT HEALTH EFFECTS OF CHRONIC HEAVY AMPHETAMINE ABUSE

Frequent injection of "speed" can result in such communicable and potentially serious diseases as viral hepatitis, septicemia, and bacterial endocarditis. These diseases spread when nonsterile needles are shared. Abscesses, phlebitis, and infections may occur at or around the sites of injection because of incorrect injection technique, nonsterile needles, or repeated injections at the same spot. Collapsed blood vessels are also possible, and blockage of blood vessels is common among those who inject street preparations, which may contain insoluble particles which can lodge in the small blood vessels of the extremities, lungs, and brain.

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[4] It is worth noting that many heavy users are aware that their thinking is often paranoid, and some even dismiss it as the price they are willing to pay for continuing their habit.

A generally poor state of health and lowered resistance to disease is common among heavy users. Their condition is usually due to such indirect effects as poor nutrition, postponement of adequate medical treatment, and insufficient sleep.

LETHALITY

Deaths directly resulting from acute overdose of amphetamines are extremely rare. Indeed, in the world literature up to 1979, only 79 cases of death due either to the pharmacological actions of amphetamines or to secondary complications related to the route of administration had been reported (Kalant & Kalant, 1979). The lowest known single dose resulting in death was 120 mg administered intravenously; nontolerant persons have been known to survive doses of several hundred milligrams, and tolerant individuals, several grams. Causes of deaths which have been attributed to amphetamine overdose include (1) cerebrovascular collapse (collapse of the blood vessels in the brain) due to sudden extreme elevation of blood pressure, (2) acute cardiac failure, and (3) hyperthermia (extremely high fever).

Deaths related to secondary complications of intravenous administration have been caused by acute bacterial endocarditis, viral hepatitis, necrotizing angiitis (small blood vessel deterioration, including rupture of the vessels supplying the brain), foreign-body reactions, and very occasionally other pathologic conditions unrelated to the specific actions of amphetamines.

However, the number of unknown amphetamine-linked deaths from other causes is undoubtedly significantly higher. Numerous violent and sometimes bizarre accidents, homicides, and suicides have been documented, and case reports appear to indicate that many of those involved were suffering from amphetamine psychosis at the time of the violent episode. Homicide victims have ranged from close relatives and amphetamine co-users to complete strangers. Both suicide attempts and successful suicides have occurred under heavy intoxication with amphetamines and during or after withdrawal. As well, some deaths are probably attributable to disease indirectly resulting from lifestyle.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance to many of the significant effects of amphetamines has been reported to develop when these drugs are chronically administered. Cross-tolerance between amphetamines and other amphetamine-like CNS stimulants has been clinically observed. There does not appear to be cross-tolerance with cocaine.

Appetite Suppression: Substantial clinical and research evidence reveals that tolerance to the appetite-suppressant (anorectic) effect of amphetamines can develop rapidly. However, in low-dose users, individual differences are reported to be considerable regarding the degree to which tolerance is developed and sustained with protracted use. Much of the information pertaining to tolerance in chronic high-dose users is based on unsystematic clinical observations or anecdotal reports.

Sleep Disturbance Effects: Tolerance to the sleep-disturbing effects, including disturbance of REM (rapid eye movement) sleep, appears to at least partially develop, and it has been reported that even in high-dose users sleep is substantially less impaired as chronicity develops. However, it is also reported that reliance on sleeping aids such as sedative/hypnotic drugs is pervasive among chronic users.

Euphoric Effects: The euphorogenic and other mood-elevating effects of amphetamines appear to be subject to the rapid development of tolerance, particularly in the case of "speeders." Many users report having increased their daily dose several times over the course of their drug-using career in order to maintain or increase the pleasurable effects of the drug. During a "run," speeders report that a "rush" occurs only during the first "hit" (injection) and that the intensity of pleasurable effects upon successive injections rapidly diminishes. Significantly, the daily dose ultimately reaches a plateau beyond which no further dose increase can produce the desired effects. Indeed, with uninterrupted use, pleasurable effects can give way to dysphoria, paranoid thinking, or even psychosis. However, following a period of abstinence, the desired effects can once again be achieved. Therefore, the occasional user is less affected by tolerance than the regular user.

Other Effects: Tolerance has also been reported to develop to the following effects: dilation of the pupils, mild hyperthermia (increased body temperature), increased blood pressure and heart rate, increased respiratory rate, and increased energy (progressively expressed as agitation and restlessness). Tolerance to the psychosis-producing effects of amphetamines has not been reported.

Like methylphenidate (e.g., Ritalin), amphetamines produce a calming effect in many hyperkinetic children, who suffer from an abnormally high level of undirected motor activity. Under the influence of these drugs, their behavior is observed to be very much more directed and less erratic. Fortunately, children do not develop tolerance to this particular effect of these stimulants, although why they do not is not fully understood. Those who suffer from narcolepsy (frequent inappropriate and uncontrollable sleeping episodes) usually respond favorably to amphetamines. In their case also, neither tolerance to the anti-narcoleptic effect nor physical dependence appears to develop even after years of continued use.

Physical Dependence/Withdrawal

Most experts agree that chronic high-dose use of amphetamines results in physical dependence and a characteristic withdrawal sickness. When chronic use is abruptly discontinued, the clinical picture of withdrawal does not include major grossly observable physiological disruptions. Rather, the prominent symptoms are extreme fatigue followed by prolonged but disturbed sleep. Upon awakening, the appetite is quite voracious. Irritability, lassitude, and moderate to very severe emotional depression also typically occur. Occasionally, sleep disturbances and psychotic symptoms may persist after the period of prolonged sleep. However, the syndrome usually clears after several days of abstinence.

The above symptoms are most likely to be particularly intense after a "run" of several days involving repeated very high doses, a pattern not unusual among "speeders." Thus "speeders" may undergo withdrawal on a number of occasions, the pattern being a "run" followed by a "crash" followed by a "run."

Withdrawal effects, particularly depression, can be reversed by taking more of the drug, and this is a major reason for readministration during the withdrawal phase. The principal risk in readministration is the recurrence of psychotic symptoms.

Psychological Dependence

Marked psychological dependence frequently results even among regular low-dose users, according to most reliable sources. In this case, psychological dependence is characterized by a preoccupation with and compulsive need to continue taking the drug because of those psychological effects which the user deems to be favorable. The user usually ignores such questions as medically therapeutic benefit (in the case where the drug is prescribed) and possible adverse and unpleasant side effects. Certain of the drug effects are craved so intensely that, if the drug is temporarily unavailable, severe distress or even feelings of panic are experienced.

Clinicians have also noted in psychologically dependent users that a pleasurable response (relaxation of tension, a generally "good" feeling) can result from the specific act of taking the drug, before its pharmacological actions are felt. Furthermore, the highly pleasurable effects may be so associated in the user's mind with the act of administration that some "speeders" can enjoy injecting even pharmacologically inert substances.

PATTERNS OF USE

Amphetamine abuse peaked between the 1950s and the early 1970s, having reached epidemic proportions mainly among young people under 25 in North America, parts of Europe, and Japan. Although the abuse of amphetamines is still of very serious concern to medical and legal authorities, surveys taken in the mid to late 1970s indicate that amphetamine abuse, although still common, is on the decline. Several factors appear to be associated with this decline.[5]

Decline in Medical Use

1. Many early claims of their potential therapeutic value were either unfounded or greatly exaggerated (e.g., in the treatment of conditions ranging from alcoholism to bed wetting).
2. Officials of health associations, governments, and the pharmaceutical industry replaced them with weaker substances where possible because of the growing alarm over their extremely widespread abuse. Up to that point they were easily available.
3. Reports in medical journals of addiction resulting from medical use, of serious poisoning particularly in children, and of other adverse effects in adults led to increasingly greater caution in prescribing amphetamines.
4. In some cases even where some possible therapeutic benefit could be ascribed to the clinical use of amphetamines (e.g., the control of obesity), the valid concern over the disadvantages

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[5] From the peak legal production of some 12 billion doses of amphetamines in the U.S. alone in 1971.

and the availability of newer drugs believed to be safer prompted government officials to prohibit completely prescribing them for such conditions.

Decline in Nonmedical Use (Including Prescription Abuse)

1. Legal production has been reduced and more tightly controlled. As a result, there are fewer legally produced amphetamines that could be diverted to illegal use.
2. Greater control has been established by government over legal dispensing practices.
3. According to street drug analysis surveys, there has been a trend over the past several years toward reduced quality of illicitly produced amphetamines and a lower demand for the inferior product.
4. Related CNS-stimulant drugs producing similar effects have become available from both licit and illicit sources; these drugs are both more easily obtained and of a more dependable and consistent quality than illicitly produced amphetamines.

While the newer CNS-stimulant drugs are increasingly replacing the amphetamines, many of these drugs can produce a similar spectrum of adverse effects at therapeutic levels and when taken in high doses or chronically abused.

ABUSE POTENTIAL

Dependence Liability

Among central nervous system drugs of abuse, the dependence liability of methamphetamine and amphetamine is considered to be extremely high.[6] Both can produce powerful euphoria. (Experienced users claim that the euphoric and stimulant properties of methamphetamine are greater.) Because both are soluble in their pure form, they can be administered in large amounts by injection directly into the bloodstream; intravenous injection permits very rapid and intense gratification.

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[6] Dependence on injectable methamphetamine can be so profound that relapses among users who have undergone a period of sustained abstinence are the rule and their prognosis for recovery is at least as bad as in narcotic analgesic dependence.

Inherent Harmfulness

Inherent harmfulness is not a significant factor in deterring abuse of these drugs. At usual dose levels their potentially hazardous effects are not ordinarily manifested. However, as noted earlier, many experienced abusers, particularly of injectable methamphetamine, frequently engage in repeated very high dose administration; they are generally aware of the heightened risks and are also willing to accept them. In fact, the willingness of high-dose abusers to embark on a "run" seems hard to credit, for they know from past experiences that, after early exhilaration, continued administrations are very likely to result in increasingly severe psychic and physical distress.

Availability

For the several reasons cited above under Patterns of Use, the abuse potential of the amphetamines is now greatly restricted because of the drastic reduction in their availability over the past decade.

REFERENCE

Kalant, H., and Kalant, O.J., Death in amphetamine users: causes and rates, in *Amphetamine Use, Misuse and Abuse*, D.E. Smith et al. (Eds.), G.K. Hall and Co., Boston, 1979.

Antihistamines

DRUG CLASS: HISTAMINE ANTAGONISTS

SYNOPSIS

Antihistamines are a chemically heterogeneous class of drugs which can block the effects of histamine, a naturally occurring substance found in cell tissue throughout the body. Histamine is released from the cells when the body experiences a hypersensitivity reaction (i.e., an allergic reaction), or when cells are injured, or in reaction to a variety of drugs and poisons. Histamine then causes the flushing, itching, and other unpleasant symptoms associated with allergic reactions, and also causes excessive bronchial and gastric secretions and a number of other undesired effects. Antihistamines are selective in their ability to block certain histaminic actions; therefore, certain antihistamines are particularly useful in treating the symptoms of a variety of allergies, while others are more effective in treating duodenal ulcers caused by the excessive secretion of gastric acids. Certain antihistamines are more effective than others in combating such symptoms of motion sickness as nausea and vomiting. Many antihistamines produce drowsiness and sedation as side effects, and some are therefore employed in a number of over-the-counter products marketed throughout the world to promote sleep and relaxation. In Canada, only diphenhydramine is sold in over-the-counter products intended for these purposes. Antihistamine products are only mildly effective when compared to sedative/hypnotic prescription products used for the same purposes.

Many people underestimate the potentially toxic effects of antihistamines on young children and fail to store the drugs safely out of reach. Several children have been accidentally and seriously poisoned and some have died, although in Canada in recent years there have been no child deaths attributed to antihistamine overdose. Large quantities of antihistamines can also be hazardous to adults, particularly when they are taken in combination with other central nervous system depressants.

Antihistamines taken alone produce little euphoria; however, it appears that some antihistamines enhance the pleasurable effects of alcohol and other CNS-depressant drugs of abuse. For this reason, and because they are easily available, antihistamines have a moderate abuse potential.

DRUG SOURCE

Antihistamines are produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Trade names of some of the commonly used antihistamines include:

- dimenhydrinate—Dramamine, Gravol;
- diphenhydramine—Benadryl, Nytol, Sominex;
- tripelennamine—Pyribenzamine;
- cimetidine—Tagamet.

STREET NAMES

None in common use.

COMBINATION PRODUCTS

Antihistamines are ingredients in many prescription and over-the-counter cough-suppressant medications, analgesics, cold and congestion preparations, and antiallergic and antispasmodic products.

One combination product of particular interest is Mandrax (methaqualone and diphenhydramine), which is medically used to promote sleep.[1] Mandrax has been widely abused both in North America and in Europe. On the street, it is referred to as mandrakes and mandies.

Street drug combinations include blue velvet (paregoric and tripelennamine) and Ts and Blues (pentazocine and tripelennamine).

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[1] Methaqualone is a sedative/hypnotic drug: see article below.

MEDICAL USES

1. Many, but not all, antihistamines are effective in combating the symptoms associated with certain types of allergic reactions, such as hay fever.
2. Several antihistamines can produce drowsiness and sedation, and some are marketed specifically for those properties. Diphenhydramine preparations for sedation and for sleep induction are available over the counter in most Canadian pharmacies.[2]
3. Both diphenhydramine and dimenhydrinate (among several other antihistamines) are effective in combating the common symptoms of motion sickness and of radiation sickness, such as nausea and vomiting.
4. Cimetidine is used in the treatment of disorders resulting from excessive secretion of gastric acid, such as duodenal ulcer.
5. Some antihistamines (e.g., diphenhydramine) are useful antispasmodic agents.

The relative value of antihistamines for symptomatic relief from head colds has been questioned by some; while they relieve runny nose, their drying effect may actually be harmful to the sensitive mucosal membranes lining the upper respiratory tract in some cases, and the result may be an itchy dry cough.

PHYSICAL APPEARANCE

Most antihistamines occur as white, odorless crystalline powders which have a bitter taste; they vary considerably with regard to their solubility in water and alcohol.

DOSAGE

Medical

Dosage for the treatment of a particular disorder varies, depending on the antihistamine chosen or prescribed and the severity of the condition. The following are examples of typical therapeutic doses of commonly used products:

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[2] For sedative and sleep-inducing properties, antihistamines are not as potent as any of the sedative/hypnotic agents which require a doctor's prescription.

- for combating the symptoms of hay fever and similar allergic conditions—50 mg of tripelennamine up to four times per day;
- for induction of sleep—25–50 mg of diphenhydramine at bedtime;
- for combating motion sickness and other forms of nausea—50–100 mg of dimenhydrinate up to four times per day;
- for combating duodenal ulcer—300 mg of cimetidine four times per day with meals and at bedtime.

Nonmedical

Little is known about the nonmedical use of antihistamines; however, it has been reported that at least some of these drugs produce hallucinations at high dose levels, and there are a few cases of deliberate ingestion of dimenhydrinate at very high dose levels (e.g., 800 mg) to achieve hallucinogenic effects.

With very regular use for an extended period, tolerance may develop to the sleep-inducing effects of antihistamines. Higher than the recommended nightly doses may then become necessary if the tolerant user wishes to maintain these effects. With occasional use, or use for brief periods (such as a few consecutive nights), however, tolerance is unlikely to develop.

ROUTES OF ADMINISTRATION

Most antihistamines are administered orally by tablet or capsule or in solution; however, injection may be used in the emergency treatment of severe allergic reactions. The street drug combinations noted above are usually injected intravenously.

EFFECTS OF SHORT-TERM USE: LOWER DOSES[3]

HISTAMINE AND ANTIHISTAMINES

Histamine is a naturally occurring substance found in almost all body tissue; its concentration is particularly high in the cells of skin tissue, the lungs, and the intestinal mucosa. The release of histamine can be brought about under several conditions, such as hypersensitivity (allergic) reactions, cell injury, and a range of drugs and poisons (e.g., bee venom). When released, histamine is thought to interact with certain cells in the body (histamine receptors) to cause a number of effects. Some key actions include: (1) stimulation of the smooth muscles, (2) vasodilation in capillary beds particularly on the surface of the face and upper body (the so-called "blushing area"), which causes flushing, a rise in skin temperature, and a drop in blood pressure, (3) increased heart rate, (4) stimulation of nerve endings on the body surface, which results in itching and pain, (5) bronchial and eye secretions, and (6) pronounced gastric secretions.

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[3] Single doses within the therapeutic range taken orally by nontolerant users.

Antihistamines are substances that act to block histamine receptors, although only a few (e.g., cimetidine) effectively block those histamine receptors that stimulate excessive gastric secretions. Thus, antihistamines tend significantly to diminish (i.e., to antagonize) the effects of histamine on the body.

Below are listed the effects produced by many antihistamines, although their occurrence and intensity can vary from one substance in this class to another.

CNS, behavioral, subjective: drowsiness; dizziness; mild impairment of concentration; mild motor incoordination; lassitude; sedation or sometimes insomnia; excitation and nervousness (more commonly in children than in adults); mild euphoria; blurred vision; ringing in the ears; and infrequently tremors.

Cardiovascular: palpitation; headache; reduced blood pressure.

Respiratory: dryness of the nasal, throat, and other respiratory passages; cough.

Gastrointestinal: dryness of the mouth; gastric discomfort; loss of appetite; relief from nausea or increased nausea and vomiting; constipation or diarrhea.

Other: frequent urination; heaviness and weakness in the hands; muscle pain; tightness in the chest.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[4]

Intensification of the low-dose effects may occur. Sleep is the most probable result, following drowsiness, lethargy, and sedation. When taken in combination with alcohol or other CNS-depressant drugs, effects tend to be intensified.

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[4] Single doses in excess of the therapeutic range taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

The effects of very high doses (i.e., overdose) on children (as few as 15–20 tablets of most over-the-counter antihistamines) can be extremely severe. Symptoms include flushing; fixed and dilated pupils; agitation; muscle incoordination; hallucinations; very high fever and convulsions. These symptoms may be followed by coma, profound cardiovascular and respiratory depression, and sometimes death.

The effects of very high but nonlethal overdose on adults can include: confusion; toxic psychosis characterized by hallucinations, delusions, and disorientation; tremors; muscle twitching; irregular heartbeat; abnormally high blood pressure; and, rarely, convulsions.

EFFECTS OF LONG-TERM USE

When antihistamines are used regularly at therapeutic dose levels, adverse effects are generally mild and tend to be similar to short-term low-dose effects. However, with chronic regular use, the effectiveness of the drugs appears to diminish. Regular topical application of certain antihistamines can cause allergic skin rashes.

Little is known about the effects of chronic high-dose abuse.

LETHALITY

As with ASA, parents often underestimate the danger of antihistamines to very small children. Failure to store the drugs out of children's reach has led to accidental poisonings. Overdoses of 30–60 mg per kilogram of body weight can be lethal to very young children.

The margin of safety for adults is considerably greater than for children; nonetheless, deaths of adults have resulted from severe overdose of antihistamines, although most of these deaths involved simultaneous overdose of other drugs (usually sedative/hypnotics). Lethal overdoses of antihistamines in adults have produced coma followed by a period of hyperexcitability, often including delirium and convulsions. The terminal phase is characterized by severe CNS depression, and death results from respiratory arrest and/or cardiovascular collapse. Because antihistamines are so commonly found in household medicine cabinets, they have often been used in suicide attempts.

TOLERANCE AND DEPENDENCE

Chronic use of antihistamines results in an increased capacity of the liver to metabolize the drugs; their effectiveness is thus decreased, and if the user wishes to maintain certain desired effects, then an increase in daily dose is required. Tolerance can develop to the sleep-inducing and sedating effects when antihistamines are used on an everyday basis for an extended period. When an antihistamine is regularly used for its psychoactive effects, users may become psychologically dependent: that is, they develop a craving for the psychological effects and a sense of urgency with regard to maintaining an adequate supply of the drug.

Current evidence pertaining to whether physical dependence on antihistamines may be acquired with chronic very regular abuse is insufficient to justify conclusions one way or the other.

PATTERNS OF USE

Products containing antihistamines are so commonly used for such a variety of purposes that at least one antihistamine product is likely to be found in the medicine cabinet of most North American homes. Antihistamines, either alone or in combination preparations, are easily available over the counter and by prescription. In many instances the identical antihistamine is marketed for a number of different purposes. For example, in Canada diphenhydramine is found in cough and cold preparations, antiallergic preparations, and sleep-promoting preparations. It can also be used for relief from the symptoms of motion sickness.

Some jurisdictions (e.g., the state of California) have recently passed legislation to prohibit driving an automobile when using antihistamines because of the sedation and drowsiness they produce.

The Canadian Medical Association has expressed concern over the easy availability of many products containing antihistamines. It recommends that pharmacists have greater control over consumers' access to these drugs.

Antihistamines alone are rarely taken by street drug abusers; however, it is not unusual for these drugs to be consumed in combination with other CNS depressants, such as alcohol, because some antihistamines seem to enhance the desired effects of the latter.

ABUSE POTENTIAL

The dependence liability of antihistamines is low; they produce little euphoria, and what little is produced rapidly decreases with regular use. However, their abuse potential is moderate because of their easy availability to those who would abuse them (1) to enhance the effects of other drugs and (2) to intensify the mild sedation and drowsiness many of them produce.

Barbiturates

DRUG CLASS: SEDATIVE/HYPNOTICS

SYNOPSIS

Barbiturates are potent central nervous system (CNS) depressants. At low doses, these drugs generally induce a state of relaxation and tranquility and can mildly impair cognitive and motor functions. At moderate doses, they can both induce sleep and increase the amount of uninterrupted sleep time. However, prior to the onset of sleep or on occasions when sleep does not result, cognitive and motor functions can be moderately impaired and many users experience a state of pleasurable intoxication. At even higher doses barbiturates induce anesthesia—a state of unconsciousness wherein even such powerful stimuli as severe pain are not experienced. At these levels a more severe condition of impairment and intoxication (similar to that induced by large amounts of alcohol) typically precedes unconsciousness. As the size of the dose increases, barbiturates also cause ever greater depression of the respiratory control centres of the brain. This last action constitutes the major toxic effect of barbiturates; indeed, many overdose deaths have resulted from respiratory arrest.

There are more than a dozen barbiturates in clinical use, prescribed by physicians for a variety of purposes. The choice of a drug for a specific clinical purpose is partly based on its duration of action—the ultrashort-acting barbiturates only for induction of anesthesia; the short- and intermediate-acting agents for sedation and sleep induction; and the long-acting agents to control epileptic seizures and for prolonged sedation and occasionally for sleep induction.

In addition to therapeutic uses, barbiturates are also subject to widespread abuse for their pleasurably intoxicating effects. Because tolerance to the desired effects can develop very rapidly with regular use, higher daily doses become necessary to maintain the effects. However, taking progressively higher doses of barbiturates to compensate for acquired tolerance can lead to life-threatening complications: on the one hand, there is the risk of death from overdose; on the other hand, when chronic and regular high-dose abuse has resulted in profound physical dependence, abrupt withdrawal can present symptoms so severe as to cause death. The barbiturates are for this reason considered to be among the most dangerous of the widely abused drugs.

Because of the risks associated with barbiturate abuse, and because new and safer drugs such as the benzodiazepines are now available, barbiturates are less frequently prescribed than in the past. Nonetheless, they are still widely available both to legitimate users and to abusers.

DRUG SOURCE

Barbiturates are produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Examples of the nonproprietary names of some commonly used barbiturates (in the form of their salts) along with their trade names include:

- amobarbital sodium—Sodium Amytal;
- butabarbital sodium—Butisol Sodium;
- pentobarbital sodium—Nembutal;
- phenobarbital sodium—Luminal;
- secobarbital sodium—Seconal.

STREET NAMES

There are literally dozens. Some of the more common street names applied to all barbiturates include barbs, downers, and goofballs.

Many individual barbiturates are named for the colors of the trade products. Examples of names include blues or blue heavens (Sodium Amytal), yellow jackets (Nembutal), red birds or red devils (Seconal), and rainbows or reds and blues (Tuinal).

COMBINATION PRODUCTS

- Tuinal (amobarbital sodium and secobarbital sodium);

- Dexamyl (dextroamphetamine and amobarbital sodium);
- Fiorinal (butalbital, codeine, ASA, and caffeine).

MEDICAL USES

Traditionally, barbiturates were classified as ultrashort-, short-, intermediate-, and long-acting, depending on their duration of action. Physicians have generally prescribed these drugs in accordance with this classification, although it is not an entirely reliable indicator of drug action.[1]

1. Ultrashort-acting barbiturates, such as thiopental sodium (Pentothal Sodium), are employed as intravenous anesthetic agents; they may be the exclusive anesthetic used in brief surgical procedures, or they may be used in longer procedures to induce anesthesia prior to another anesthetic being employed.
2. Short- and intermediate-acting barbiturates, such as secobarbital sodium and amobarbital sodium respectively, are used mainly for daytime sedation and for induction of sleep. They are also used for pre-anesthetic sedation.
3. Long-acting agents, such as phenobarbital sodium, are also used for daytime sedation and for induction of sleep, as well as to help prevent or mitigate epileptic seizures.

PHYSICAL APPEARANCE

In the form of their salts, barbiturates are generally white, bitter, odorless powders which are soluble in water.

DOSAGE

Medical

- daytime sedation—e.g., phenobarbital sodium, 15–30 mg three times per day;
- induction of sleep—e.g., secobarbital sodium, 100 mg at bedtime;

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[1] For further discussion of this subject, see Sedative/Hypnotics in the chapter Central Nervous System Depressants, section 2.

- to help prevent or mitigate epileptic seizures—e.g., phenobarbital sodium, 50–100 mg two to three times per day.

Nonmedical

Nonmedical users often take barbiturates initially at doses within the therapeutic range. As tolerance develops, users may progressively increase their daily dose to many times their original intake. To show how high such doses can get, in early research efforts, subjects under controlled conditions were able to tolerate daily doses of secobarbital sodium and pentobarbital sodium of up to 1,800 mg and daily doses of amobarbital sodium up to 3,800 mg by increasing their daily dose over a several-month period. Even higher daily doses for addicted persons have occasionally been reported; however, it must be emphasized that these extremely high doses could produce lethal results even for tolerant abusers.

ROUTES OF ADMINISTRATION

For medical use, barbiturates are administered orally by tablet or capsule or in liquid solution, rectally by suppository, or by subcutaneous, intramuscular, and intravenous injection. Administration by injection is restricted almost exclusively to medical settings, and must be undertaken with great care because of the potentially life-threatening effects. Injection is sometimes used to control seizures in emergency situations. Some street drug users, such as heroin addicts, inject barbiturates in spite of the attendant risks.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, behavioral, subjective: tranquility, relaxation, mild euphoria; reduced interest in external environment; dizziness; lethargy, drowsiness (in some cases sufficient to induce sleep); mild motor coordination impairment, particularly of fine dexterity functions; mild impairment of thought processes and of short-term memory; increased reflex reaction time; occasionally mild release of inhibition and mood swings; paradoxical excitement in some users; exacerbation of preexisting pain; and "hangover" after the barbiturate effects wear off.

Gastrointestinal: occasionally nausea, vomiting, and abdominal pain.

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[2] The therapeutically recommended dose taken orally by nontolerant users to induce sedation: i.e., 50 mg or less.

EFFECTS OF SHORT-TERM USE: MODERATE DOSES[3]

All low-dose CNS-depressant effects are intensified. These and other symptoms include:

CNS, behavioral, subjective: the onset of sleep. However, many symptoms occur prior to this or when sleep does not result: a brief period of heightened activity; a pleasurable state of intoxication and euphoria in some, although others may experience hostility, depression, and/or anxiety; oversedation and confusion; greater impairment of fine and gross motor functions, as well as of memory and thought processes; moderate release of inhibitions; mood swings. Other effects, similar to those produced by moderate amounts of alcohol, include slurred speech, disturbed vision, possibly impaired judgment, increased libido, and "hangover" after the barbiturate effects wear off.

Cardiovascular: slight drop in blood pressure and heart rate.

Respiratory: slight respiratory depression.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[4]

CNS, behavioral, subjective: progressively higher doses cause ever greater CNS depression. Onset of sleep is highly probable, and many progress to deeper levels of unconsciousness. Prior to the onset of sleep, symptoms are very similar to those exhibited by someone highly intoxicated on alcohol: exaggerated levels of activity may occur for a brief period; emotions are often intense and their expression is likely to be unpredictable and extreme; and thinking and other cognitive functions may be severely impaired, as may motor and perceptual functions.

Cardiovascular: progressive decline in blood pressure.

Respiratory: progressive respiratory depression.

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[3] The therapeutically recommended dose taken orally by nontolerant users to induce sleep: i.e., 100–200 mg, or less in particularly sensitive individuals.

[4] Single doses higher than those indicated for induction of sleep, taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

Very high doses (i.e., severe overdoses) characteristically produce slow, shallow, and irregular breathing, pupillary constriction followed by paralytic pupillary dilation, lack of responsiveness of superficial reflexes, low body temperature, very low blood pressure, weak pulse, and coma. Death may result from respiratory arrest.

EFFECTS OF LONG-TERM USE

While barbiturates can induce sleep, they also interfere with certain normal sleep processes. During normal sleep, electroencephalogram (EEG) recordings show evidence of alternating phases of slow-wave and REM (rapid eye movement) activity. During REM phases of sleep, the eyeballs continuously oscillate underneath the eyelids, skeletal muscles are highly relaxed, and if sleepers are wakened they are very likely to report that they were dreaming. In fact, almost all dreaming occurs during these REM phases.[5]

It is generally agreed that initially barbiturates significantly reduce REM sleep time. With nightly use, tolerance develops and the amount of REM sleep time gradually increases toward normalcy; however, some investigators report that it returns to a level somewhat below normal. REM sleep appears to be biologically essential, and when it is reduced, psychological impairment can occur. The impairment is usually manifested as daytime anxiety, restlessness, depression, and, occasionally, psychotic episodes. Furthermore, many regular barbiturate users complain that the quality of their sleep is poor and that they do not feel well rested upon awakening.

When administration of barbiturates is discontinued, the above effects tend to disappear rapidly. However, the person is then likely to experience a temporary "rebound" of REM sleep: that is, for a short while, REM sleep time increases to a level greater than during normal sleep. During this period (several nights), phases of REM sleep are irregular; the amount of dream time increases—dreaming may last for most of the night, with a greater probability of nightmares; and upon awakening, the person is often lethargic and irritable.

Protracted high-dose abuse tends to produce effects similar to those resulting from short-term use, not unlike a state of chronic inebriation. Effects include impaired memory, judgment, and thinking; hostility, depression, or mood swings; reduced attention span; and exacerbation of preexisting emotional disorders which may result in paranoia or suicidal thinking. Chronic fatigue associated with poor sleep or frequent insomnia may occur, as may slurred speech and impairment of fine and gross motor coordination. The following may also be manifested: visual and ocular disturbances; vertigo; increased superficial reflex reaction time; impotence; reduced libido; menstrual irregularities; and certain respiratory disorders resulting, in part, from chronic respiratory depression.

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[5] For a more extensive discussion of REM sleep and other aspects of normal sleep, see Sedative/Hypnotics in the chapter Central Nervous System Depressants, section 2.

LETHALITY

Results of an American nationwide survey taken over a three-year period (1973–76), published in 1979, indicated that barbiturates were implicated in over half of those drug-related cases labeled suicide by medical examiners.

The principal toxic effect of barbiturates (and many other CNS depressants) is respiratory depression. Although mild tolerance may develop to the respiratory-depressant effect, it develops much less rapidly than does tolerance to the desired level of pleasurable effects or to the level necessary to produce sleep. Therefore, the margin of safety between a lethal dose and a pleasure-producing dose decreases as the daily dose increases. Thus, a relatively small dose increase (e.g., 100 mg) for the regular heavy user could result in death.

The lethal dose of barbiturates for nontolerant users is not substantially less than that for heavy abusers. However, there appears to be wide variation among individuals as to what constitutes a lethal dose for a specific barbiturate; furthermore, an overdose of certain barbiturates is more likely to produce lethal results than a molecularly equivalent overdose of others. Generally, the lethal dose range is between 2 and 10 grams (2,000–10,000 mg)—the shorter-acting barbiturates (e.g., secobarbital, pentobarbital) tending to be fatal at lower doses and the longer-acting barbiturates (e.g., phenobarbital) tending to be fatal at higher doses. When taken in combination with other CNS depressants, such as alcohol or other sedative/hypnotics, the lethal dose of barbiturates can be substantially smaller.

In contrast to narcotic analgesic poisoning, for which there are antagonists capable of reversing overdose effects, there are no known antagonists for barbiturates or other sedative/hypnotics.

In addition to deaths from overdose of the drug itself, deaths in heavy dependent users have occurred as a result of withdrawal. The withdrawal syndrome is discussed below.

TOLERANCE AND DEPENDENCE

Tolerance

The many barbiturates have sufficiently differing pharmacokinetic characteristics that it is difficult to generalize about the development of tolerance among them. Furthermore, there is a wide variation among users in the rate at which tolerance develops to the same drug, and the variation does not correlate significantly with body weight. Although conclusive data are not yet available, it has been suggested that tolerance develops more rapidly to the effects of the shorter-acting barbiturates.

Tolerance can develop very rapidly to the sleep-induction and sleep-maintenance effects of barbiturates, often within a week or two of consecutive nightly administrations.[6] When high doses (in excess of approximately 400 mg) are regularly administered, tolerance to their pleasurably intoxicating effects normally develops within several days to several weeks. Those who choose to maintain any of these effects must therefore frequently increase their daily dose, and thus also increase the danger of serious adverse consequences.

With regular use, tolerance to both impaired motor coordination and slowed reaction time appears to at least partially develop. Most investigators agree that tolerance to the anticonvulsant property of phenobarbital does not occur, although the evidence is not yet conclusive.

There is a high degree of cross-tolerance among barbiturates and also between barbiturates and most other sedative/hypnotic drugs: that is, a desired effect will not result if the user who is tolerant to one of these drugs ingests another at a dose level which would otherwise be sufficient to produce the same effect.

[6] This rapid tolerance contrasts with the gradual development of tolerance over several months to the REM-sleep-depressing effects of barbiturates.

Tolerance rapidly diminishes following a short period of abstinence (a few weeks) from both barbiturates and other sedative/hypnotic drugs, and normal sensitivity is then restored.

Psychological Dependence

Psychological dependence on barbiturates can result after regular use, irrespective of the size of the dose taken. In this case, users crave the psychological effects of the drug even though they may not employ it every day. The drug takes on an exaggerated importance to users, and anxiety or even feelings of panic may ensue if they are temporarily unable to obtain an adequate supply. In fact, users will adamantly resist any attempt by others to curtail their use of barbiturates, even when they no longer produce any significant psychoactive effects. The craving may in fact persist long after drug use is terminated.

Physical Dependence/Withdrawal

Evidence suggests that even with protracted and regular use of barbiturates, significant physical dependence problems are unlikely to develop provided that daily doses are at or below the recommended therapeutic level (i.e., not above 100–200 mg per day).[7] However, a mild withdrawal sickness typically follows abrupt abstinence after chronic consumption of moderately high abusive doses (i.e., an average of 400–600 mg per day); this state is characterized by tremulousness, anxiety, weakness, insomnia, and (infrequently) convulsions.

A more severe withdrawal sickness tends to follow abrupt abstinence after chronic and regular consumption of very high abusive doses of the short-acting barbiturates (900 mg per day or more). Early symptoms appear within 12–24 hours after the last administration and can include the symptoms listed above in a more intense form as well as a rapid drop in blood pressure when attempting to stand, severe weakness, and hyperactive blink reflex and deep reflexes. The intensity of the syndrome peaks between 24 and 72 hours after the last administration, and symptoms likely to occur at this time include grand mal seizures (ranging from a single seizure to uninterrupted seizure activity), delirium, visual hallucinations, and a very high body temperature. Death can occur during this period of peak intensity and is usually caused by cardiovascular collapse or cerebral hemorrhage. Provided the person survives, the symptoms gradually decline in intensity and disappear after several days.

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[7] However, many investigators view the symptoms of REM "rebound" (which can occur after protracted use in this dose range) as withdrawal phenomena.

A severe withdrawal sickness, similar to the above, occurs after abrupt abstinence from chronic abuse of very high doses of the longer-acting agents, such as phenobarbital. However, there are some important differences: a more gradual onset of symptoms, a longer duration of symptom activity (up to two weeks), and fewer instances of grand mal seizures.

There is a high degree of cross-dependence among barbiturates and also between barbiturates and other sedative/hypnotics (including alcohol); therefore, many of these drugs, if taken in sufficient quantities, can partially or fully postpone the withdrawal sickness induced by abstinence from any of the others up to the point that delirium develops. Beyond that point, there is no known drug capable of suppressing barbiturate withdrawal.

Gradual withdrawal under medical supervision usually involves initial administration of high daily doses of phenobarbital, followed by progressively lower daily doses over a period of several weeks. Under these conditions, severe withdrawal symptoms are unlikely to be experienced.

PATTERNS OF USE

Recently, there has been a notable decline in the prescribing of barbiturates. It would appear that there are three important factors which have contributed to this trend:

- an increasing body of evidence concerning both the highly addictive properties of barbiturates and their widespread abuse;
- greater public and medical awareness of the substantial number of barbiturate-implicated deaths from suicide, accidental overdose, and severe withdrawal; and
- the availability of effective alternatives, although many are not necessarily safer.[8]

In spite of these well-known problems, it has been estimated that perhaps three to four billion doses of barbiturates are still prescribed in the United States alone each year. They are prescribed primarily for the elderly, for hospital inpatients, for those undergoing medical or emotional crises, and for those suffering from epilepsy. Approximately two-thirds of those using barbiturates under medical supervision are women.

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[8] A group of drugs as effective as barbiturates and generally accepted as much safer are the benzodiazepines; see the articles below.

Surveys of adolescent drug use indicate that barbiturates are relatively easy to obtain from home (usually prescribed for a parent or other adult member of the household), on the illicit street market, or from peers.

Barbiturates are commonly and heavily used by heroin addicts. Sometimes they combine barbiturates with the typically weak street heroin (to which they have become tolerant) and intravenously inject the combination to obtain a pleasurable "high"—a hazardous practice, as both drugs depress respiratory control centres in the brain. Some methamphetamine ("speed") abusers inject a combination of barbiturates and methamphetamine. They claim that the euphoria produced by the combination is greater than that produced by either drug taken alone. Methamphetamine abusers also take barbiturates to combat the often severe agitation resulting from repeated administrations of methamphetamine over the several days of a "run," as well as to relieve the sleep problems often associated with chronic stimulant abuse.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of the shorter-acting barbiturates is substantially greater than that of the longer-acting ones; the desired effects of the former are more rapidly and intensely experienced. Furthermore, tolerance to the pleasurable effects and sleep-inducing effects of the shorter-acting drugs appears to develop more rapidly, and therefore ever greater doses are required to produce the same effects. This state of affairs increases both the risk and severity of physical dependence.

Because the pleasurable effects of the shorter-acting barbiturates are very similar to those produced by alcohol, their dependence liability is at least as great.

Inherent Harmfulness

Few other widely encountered drugs of abuse present the extreme hazards associated with excessive use of barbiturates; both abuse and withdrawal have frequently resulted in death.

Availability

Although the medical use of barbiturates has declined, these drugs continue to be widely prescribed, and they remain easily available to the abuser through both licit and illicit sources.

Benzodiazepines I:

Chlordiazepoxide, Diazepam, Oxazepam

DRUG CLASS: MINOR TRANQUILLIZERS

SYNOPSIS

The benzodiazepine tranquillizers[1] are the most widely prescribed psychoactive drugs in the world. They are principally employed in the management of a wide range of pathological anxiety and tension states. At low to moderate doses, taken orally, they are highly effective in relieving mild to moderate anxiety and tension, and they generally do so with fewer and milder side effects than other drugs used for these purposes. At higher therapeutic doses, they can control more severe states of emotional distress.

The benzodiazepine tranquillizers have significant advantages over older agents prescribed for essentially the same purposes, such as meprobamate and the barbiturates. In addition to their fewer and milder side effects, they have the following in their favor: (1) they possess a much wider margin of safety than the older agents when taken in overdose quantities; (2) they have a generally low dependence liability; and (3) in those cases when physical dependence occurs, the withdrawal sickness precipitated by abrupt abstinence tends to be far less life-threatening than is the case with barbiturate or meprobamate withdrawal. (However, seizures do sometimes accompany severe benzodiazepine withdrawal.)

Tolerance develops to the psychoactive effects of the benzodiazepine tranquillizers when they are used very regularly. Moreover, because so many patients are maintained on these drugs for long periods of time, psychological dependence is probably quite common, and it is not unusual for users to take them to combat even the normal minor stresses of daily life. Their proliferation is in large part due to the willingness of many busy physicians to prescribe them too freely.

[1] See the next article for those benzodiazepines that are classed as sedative/hypnotics (i.e., flurazepam and triazolam).

The only benzodiazepine attractive to street drug abusers is diazepam, the one drug in the family which produces at least mild euphoria. Abusers often take it in large quantities in combination with other central nervous system (CNS) depressants such as alcohol in order to achieve a pleasurable "high." This practice is dangerous, for all of the benzodiazepines can intensify the toxic effects of other CNS depressants.

DRUG SOURCE

Benzodiazepines are produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

- chlordiazepoxide—e.g., Librium, Novopoxide;
- diazepam—e.g., E-Pam, Valium, Vivol;
- oxazepam—Serax.

Other benzodiazepine tranquillizers less widely prescribed in Canada include chlorazepate dipotassium (Tranxene) and lorazepam (Ativan).

STREET NAMES

Tranks, downers.

COMBINATION PRODUCTS

Librax (chlordiazepoxide and clidinium bromide) is used in the treatment of peptic ulcer.

MEDICAL USES

The benzodiazepine tranquillizers are currently used for:

- relief from a broad spectrum of mild to moderately severe non-psychotic anxiety and tension states other than those associated with the minor stresses of everyday life[2] (with acutely severe states, benzodiazepines may be injected intravenously);

- symptomatic relief from acute agitation, tremor, and impending delirium tremens associated with alcohol withdrawal; and
- sedation of anxious patients prior to bedtime and for induction of sleep.

Diazepam is also indicated for:

- controlling single seizures as well as prolonged seizure activity (status epilepticus) including recurrent seizures (by injection);
- adjunctively, for relief from muscle spasm associated with such neuromuscular disorders as cerebral palsy (either orally or by injection).

PHYSICAL APPEARANCE

The benzodiazepine tranquillizers occur as either colorless, white, or pale yellow crystalline powders which vary in their solubility in water and in alcohol.

DOSAGE

Medical

For relief from mild to moderate anxiety or tension states, the following dosages would be examples:

- 5–10 mg of chlordiazepoxide taken orally up to four times per day;
- 2–5 mg of diazepam taken orally up to four times per day; or
- 10–15 mg of oxazepam taken orally up to four times per day.

For more severe anxiety or tension states, the above dosages can be doubled.

For acute severe agitation and for alcohol withdrawal, 5–10 mg diazepam may be injected intravenously and repeated every three to four hours as necessary.

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[2] However, chlordiazepoxide is sometimes used in controlling acute psychotic agitation.

Nonmedical

The user may initially take daily doses within the therapeutic range. As tolerance develops, however, an increase in the daily dose is necessary to maintain the original intensity of desired effects. Highly tolerant users have been known to take daily as much as 150 mg of diazepam or as much as 600 mg of chlordiazepoxide.

ROUTES OF ADMINISTRATION

Benzodiazepine tranquillizers are most commonly taken orally by tablet or capsule or in liquid suspension. Chlordiazepoxide and diazepam are also intravenously injected where appropriate; however, neither of these drugs is effective when administered intramuscularly because they are too slowly absorbed via this route.

EFFECTS OF SHORT-TERM USE: LOW TO MODERATE DOSES[3]

RATES OF ABSORPTION AND DURATION OF EFFECTS

When taken orally, the spectrum of effects produced by any of the drugs in this family is quite similar. However, they are absorbed into the bloodstream at different rates, and the rate determines how rapidly the drug effects are experienced. Diazepam is more readily absorbed than any of the other benzodiazepine tranquillizers, its plasma concentration peaking within approximately one hour. This rapidity of absorption is the principal reason why some users of diazepam experience euphoria or a pleasant "high," and it also undoubtedly accounts for this drug's popularity among street users, who often take large quantities at one time. The relatively rapid onset of action of diazepam in comparison with other benzodiazepine tranquillizers makes it the most appropriate choice for occasional sleep induction. Oxazepam has the slowest absorption rate among the commonly used members of this drug family, taking up to three hours to reach its peak plasma concentration.

Duration of effects is determined to a significant extent by two key pharmacological factors: (1) the half-life elimination of the particular drug and (2) the half-lives of any of the psychoactive metabolites of the parent drug (i.e., those chemical products created by the metabolism of the parent drug).[4] Oxazepam, for example, generally has a short half-life in the body and none of its metabolites are psychoactive. On the other hand, both diazepam and chlordiazepoxide have longer elimination half-lives and, as well, have psychoactive metabolites which are not rapidly eliminated. Therefore, a single dose of oxazepam not only has the shortest duration of action among the benzodiazepine tranquillizers, but also does not appreciably build up in the body with repeated administrations. By contrast, a single dose of diazepam and its converted psychoactive metabolites have the longest duration of action in the body; in fact, the elimination half-life of one of its two principal psychoactive metabolites, desmethyldiazepam, is actually longer than that of the parent drug. Thus, because both diazepam and this metabolite are eliminated so slowly, repeated administrations of diazepam cause accumulations of both the parent drug and desmethyldiazepam in the body. Chlordiazepoxide holds an intermediary position between oxazepam and diazepam with regard to duration of effects.

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[3] Single doses within the therapeutic range taken orally by nontolerant users.

[4] There are, of course, substantial individual differences among users with regard to half-life durations of the same drug and its metabolites within their bodies.

CNS, behavioral, subjective: The principal desired effects are relief from anxiety and tension, relaxation, and calmness. Other effects can include mild motor incoordination; drowsiness, lethargy, fatigue; mild emotional disinhibition including hostile behavior, or emotional blunting;[5] dizziness; mild impairment of cognitive and memory functions; confusion; sometimes emotional depression; blurred vision, double vision; vertigo; slurred speech; tremors; stuttering; euphoria (occasionally with diazepam, infrequently with chlordiazepoxide, and rarely with other benzodiazepine tranquillizers).

Cardiovascular: Therapeutic doses of these drugs infrequently affect cardiovascular functions. The following have occurred in a very small percentage of patients: rapid heart rate, slight drop in blood pressure, flushing, and headache.

Gastrointestinal: nausea; constipation, urinary retention; dry mouth.

Other: changes in libido; very infrequently, allergic reactions.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[6]

The most probable effects of higher doses of benzodiazepine tranquillizers are drowsiness, oversedation, and sleep. Prior to the onset of sleep, or when sleep does not occur, the clinical manifestations may resemble a state of intoxication similar to that produced by alcohol or barbiturates; symptoms may include perceptual/motor dysfunction, impairment of motor coordination, fine and gross motor impairment; confusion; slurred speech and other articulation difficulties; slowed reflexes; impaired thought and memory (particularly short-term memory); paradoxical excitement; mood swings, hostile and erratic behavior. Some users of diazepam may experience euphoria.

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[5] Hostile behavior appears to occur rarely with oxazepam.

[6] Single doses in excess of the therapeutic range taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

These symptoms become more intense as the size of the dose increases. Jitteriness and excitation often occur when the effects of large doses begin to wear off.

At very high doses (i.e., overdose), deep sleep may sometimes progress to stupor or coma. Significant cardiovascular and respiratory depression tends to occur only at extremely high doses; however, these hazardous symptoms may occur at lower doses when benzodiazepine tranquillizers are taken in combination with other CNS depressants such as alcohol or barbiturates.

EFFECTS OF LONG-TERM USE

The longer-acting benzodiazepine tranquillizers, diazepam, and chlordiazepoxide accumulate slowly in the body and do not reach peak concentrations until several days after the commencement of daily therapy; thus their maximum therapeutic benefits, as well as the peak intensity of their undesired effects, may not be noticeable until after a number of days of therapy have passed.

Effects which sometimes persist in long-term users taking daily therapeutic doses include lethargy and oversedation, as well as decreased motivation; this last symptom generally takes the form of increased indifference to one's surroundings. The patient may also experience irritability, vivid or disturbing dreams, nausea, headache, skin rash, impairment of sexual functioning, and in women menstrual irregularities. Increased appetite and consequent weight gain may also occur.

The effects of chronic abuse (i.e., taking daily doses in excess of the therapeutic maximum) can vary considerably among individual users. Clinical observations suggest that some tolerant abusers take excessively large doses without significant overt manifestations of intoxication. However, other abusers experience symptoms similar to those caused by chronic sedative/hypnotic intoxication, and any or all of the following may occur: thinking and memory impairment, disorientation, confusion; slurred speech and other articulation difficulties; muscle incoordination and muscle weakness; dizziness; anxiety; insomnia and other sleep disorders; tremors; and emotional depression. Emotional instability and emotional disinhibition may also occur and can be manifested as outbursts of hostility or even rage; these hostile outbursts, however, are less accentuated in those taking oxazepam, presumably because oxazepam produces less emotional disinhibition than is the case for the other benzodiazepine tranquillizers.

LETHALITY

Benzodiazepines are among the most commonly implicated substances in drug overdose situations, accidental or otherwise. In fact, 31% of all overdose cases admitted to hospital emergency departments in Toronto in 1975 involved benzodiazepines. Fortunately, these drugs have a very wide margin of safety when taken alone, and deaths resulting from overdose of any of them exclusively are very rare. Enormous overdoses of benzodiazepines are generally necessary to cause dangerous levels of respiratory and cardiovascular depression.[7] However, the risk of lethal consequences can be significantly enhanced when the benzodiazepine overdose is taken in combination with large doses of alcohol, barbiturates, or other CNS depressants; such toxic combinations have resulted in a number of deaths, by both accident and suicide.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance develops to the anxiety- and tension-relieving effects (and unwanted side effects) of the benzodiazepine tranquillizers when they are chronically and regularly taken. If users wish to continue to experience the desired intensity of effects, they must increase their daily dose. For abusers of these drugs, a pernicious cycle often develops: increased tolerance, escalation of daily dose, additional increase in tolerance, further escalation of daily dose, and so on. Users may also regain their pretolerance sensitivity after a period of several weeks of complete abstinence from the specific benzodiazepine they regularly

[7] Very rapid intravenous injection of benzodiazepines also sometimes causes hazardous depression of respiratory and/or cardiovascular function.

use, as well as from all other benzodiazepines and from certain sedative/hypnotic drugs such as barbiturates, methaqualone, and alcohol. There is a high degree of cross-tolerance among the benzodiazepines and also between benzodiazepines and the above-noted sedative/hypnotic drugs:[8] that is, once tolerant to a specific effect produced by a given benzodiazepine, the user will also be tolerant to the same effect produced by an equivalent dose of any of these other drugs.

Psychological Dependence

Psychological dependence on benzodiazepine tranquillizers can occur in users irrespective of the size of the daily dose taken. The phenomenon is probably quite common among long-term regular users. Dependent users tend to experience a persistent craving for the psychological effects and feel a compulsive need to continue to take the drug even when it no longer produces any significant psychoactive effects. The drug takes on magnified importance in the daily life of the psychologically dependent user, and anxiety or even feelings of panic may ensue if it is temporarily unavailable.

Physicians often unwittingly contribute to their patients' psychological dependence by their willingness to continue to prescribe benzodiazepines for extended periods of time rather than exploring with their patients drug-free means of coping with stress. One group particularly at risk of dependence is recovering alcoholics; yet it is quite common for these patients to continue to receive benzodiazepines on a long-term basis after withdrawal from alcohol has been completed.

Physical Dependence/Withdrawal

It is generally acknowledged that among the millions of patients who regularly take benzodiazepine tranquillizers the incidence of physical dependence is very low. Many researchers and clinicians have expressed doubt that a state of true physical dependence can occur when these drugs are taken at daily dose levels within the therapeutic range even for protracted periods of time. However, chronic and regular administration usually at daily doses substantially in excess of the therapeutic range has resulted in several cases of physical dependence. Most of these cases involve diazepam and chlordiazepoxide. The withdrawal syndrome after abrupt abstinence is often not nearly as severe as that associated with withdrawal from most other

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[8] The degree of cross-tolerance between the benzodiazepines and alcohol is not as great as for these other sedative/hypnotics.

CNS depressants. An important mitigating factor is that both of these benzodiazepines are slowly eliminated from the body, and the user thus is allowed some time for gradual physiological readjustment after abrupt termination of use. In the majority of cases, withdrawal symptoms emerge within three to six days after the last dose and may include agitation, nausea and vomiting, abdominal pain, excessive sweating, tremulousness, irritability, insomnia and other sleep dysfunctions, dizziness, and loss of appetite. When long-term abuse of benzodiazepines has involved extremely high daily doses, the above symptoms are typically more intense; more severe symptoms may also occur, including abnormally high body temperature, delirium, hallucinations, delusions, muscle twitches, and grand mal seizures. However, no deaths have been reported in persons undergoing benzodiazepine withdrawal.

The typical medical treatment for benzodiazepine withdrawal substitutes a gradual withdrawal for abrupt abstinence. The procedure involves the initial administration of high daily doses of diazepam or chlordiazepoxide, with progressive reduction of the daily dose over a period of two to three weeks. Under these conditions, the severity of withdrawal symptoms is reduced considerably.

PATTERNS OF USE

Benzodiazepines are the most widely prescribed psychoactive drugs in the world. For example, in Canada these drugs are prescribed for one in every 10 persons each year, and among hospital inpatients over 30% are given a benzodiazepine drug at some time during their hospital stay (Ban et al., 1981). In the United States during the mid-1970s pharmacists filled over 70 million prescriptions per year for either diazepam or chlordiazepoxide—diazepam being the most popular and accounting for almost 60 million of these prescriptions. The principal consumers are women and middle-aged and elderly patients. Many recovering alcoholics and some narcotic analgesic addicts also receive these drugs on a continuing basis during and after completing withdrawal or while participating in methadone maintenance programs. However, there is no evidence that maintenance on benzodiazepine tranquillizers reduces the risk of relapse for these patients. In fact, some methadone maintenance patients have been known to take diazepam in abusive doses in order to create a pleasant "high."

Diazepam is the only benzodiazepine in current use which produces euphoria sufficient to be attractive to the street drug user, although in therapeutic doses this effect tends to be slight. The abuser usually takes diazepam in large doses and frequently in combination with other CNS depressants such as alcohol—a dangerous practice.[9] The use of such drug combinations seems to be widespread, particularly among young people who cannot afford to purchase more expensive drugs of abuse. Because diazepam is so widely prescribed, and is therefore found in so many North American households, it (or another benzodiazepine) is frequently among the psychoactive drugs first encountered by young people.

ABUSE POTENTIAL

Dependence Liability

With the exception of diazepam, which has a relatively low dependence liability, the benzodiazepine tranquillizers produce little or no euphoria; therefore, given the normal meaning of dependence liability, these other benzodiazepines have an extremely low dependence liability. However, psychological dependence on benzodiazepine tranquillizers is fairly common among the large numbers of people who take these drugs regularly for extended periods of time; that is, they feel the need to continue their daily use long after the drug's therapeutic value has been virtually exhausted. Furthermore, many patients have come to rely on these drugs excessively to suppress even the minor natural stresses of everyday life, and this reliance seems to reinforce their dependence.

Inherent Harmfulness

The margin of safety for these drugs is among the highest for all commonly used psychoactive drugs, even when taken in overdose quantities. Critics who believe that benzodiazepine tranquillizers are substantially overprescribed point to their low inherent harmfulness as the principal reason for the willingness of many physicians to prescribe them freely.

Availability

Benzodiazepine tranquillizers are the most widely prescribed psychoactive drugs in the world. Their easy availability contributes to their relatively high abuse potential.

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[9] Chlordiazepoxide is also occasionally taken in combination with other CNS depressants; however, street users rarely take chlordiazepoxide alone.

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Ban, T.A., Brown, T.W., DaSilva, T., Gagnon, M.A., Laurent, C.T., Lehmann, H.E., Lowy, F.H., Ruedy, J., and Sellers, E.M., Therapeutic review: Therapeutic monograph on anxiolytic-sedative drugs, *Canadian Medical Association Journal*, 124:1439-1446, 1981.

Benzodiazepines II:

Flurazepam and Triazolam

DRUG CLASS: SEDATIVE/HYPNOTICS

SYNOPSIS

The sedative/hypnotic benzodiazepines,[1] flurazepam and triazolam, are widely used drugs in the short-term management of sleep dysfunctions (such as insomnia); this is the only purpose for which they are currently prescribed. They are popular for several reasons: (1) they are effective in inducing sleep; (2) with nightly use, they retain their sleep-inducing effectiveness for a longer period of time than other drugs in this class; (3) they have a wide margin of safety even when taken in overdose quantities; (4) they have a low inherent dependence liability; and (5) their abuse potential is negligible or very low. Furthermore, they do not significantly affect REM sleep, a necessary phase of normal sleep which is adversely affected by most other sedative/hypnotic drugs.

DRUG SOURCE

Flurazepam and triazolam are produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

- flurazepam—Dalmane, Novoflupam, Somnol;
- triazolam—Halcion.

STREET NAMES

None.

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[1] See the previous article for those benzodiazepines that are classed as minor tranquillizers (i.e., chlordiazepoxide, diazepam, and oxazepam).

COMBINATION PRODUCTS

None.

MEDICAL USES

For short-term management of insomnia.

PHYSICAL APPEARANCE

Flurazepam occurs as a pale yellow crystalline powder very soluble in water and freely soluble in alcohol. Triazolam occurs as a white crystalline powder poorly soluble in water and soluble in alcohol.

DOSAGE

Medical

For induction of sleep—15–30 mg flurazepam at bedtime, or 0.25–0.5 mg of triazolam at bedtime.

Nonmedical

Little is known about the nonmedical use of either of these drugs. However, it is reasonable to assume that some regular long-term users of flurazepam and triazolam increase the size of their nightly dose to compensate for acquired tolerance to the sleep-inducing effects.

ROUTES OF ADMINISTRATION

These drugs are administered orally.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, behavioral, subjective: induction of sleep. Prior to the onset of sleep or when sleep does not occur, the following may be manifested: dizziness, lightheadedness, sometimes confusion; impaired motor coordination; concentration difficulty; mild impairment of memory; infrequently, nervousness; and blurred vision.

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[2] Single doses within the therapeutic range taken orally by nontolerant users.

Morning and daytime drowsiness frequently occur, more commonly with flurazepam than triazolam.

Cardiovascular: headache. Flurazepam sometimes produces abnormally rapid heartbeat and sweating.

Gastrointestinal: dry mouth, nausea, abdominal discomfort; loss of appetite; and less commonly vomiting and diarrhea.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

CNS, behavioral, subjective: The onset of deep sleep is the most probable effect; prior to the onset of sleep or when sleep does not occur, other low-dose effects are likely to be intensified.

At very high doses (i.e., overdose), deep sleep can progress to stupor or coma. Depression of respiratory and cardiovascular functions tends to be relatively mild except when extremely high doses are ingested.

EFFECTS OF LONG-TERM USE

Flurazepam is very rapidly metabolized by the liver and the intestine; however, a principal metabolite, desalkylflurazepam, thought to be largely responsible for the drug's psychoactive effects, is eliminated from the body slowly, particularly in elderly patients. Therefore, with consecutive nightly administrations of flurazepam, this metabolite accumulates in the body. This action reportedly accounts for the frequent observation that the maximum sleep-inducing effects of flurazepam are not achieved until the second or third night; that is, peak concentrations of desalkylflurazepam in the body are not reached after the first dose. The accumulation of desalkylflurazepam is also thought to cause the common daytime residual effects associated with the first few days of flurazepam therapy (e.g., lethargy and drowsiness). These problems do not occur with triazolam, because triazolam and its principal active metabolite are rapidly eliminated from the body.

Therapeutic doses of triazolam and low therapeutic doses of flurazepam (e.g., 15 mg), taken nightly, do not appreciably interfere with REM sleep, a problem commonly associated with most other sedative/hypnotic drugs. REM sleep is a phase of normal sleep characterized by constant oscillation of the eyeballs, continuous dreaming, and extreme muscle relaxation; reduced REM sleep time can have harmful psychological effects. In the case of those other drugs which do interfere with REM sleep, a REM rebound generally occurs after the abrupt termination of their use. REM rebound ordinarily involves an abnormal increase in the nightly amount of REM sleep time for a period of several days or even weeks; during this period, the person may suffer daytime restlessness and irritability. The fact that triazolam and flurazepam have only a minimal affect on REM sleep is one principal advantage over other commonly prescribed sleep-inducing drugs.

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[3] Single doses above the therapeutic range taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

LETHALITY

Deaths resulting from overdose of sedative/hypnotic benzodiazepines taken alone are very rare; in fact, none have been reported for triazolam. In contrast to most other sedative/hypnotic drugs, significant respiratory and cardiovascular depression tend to occur only in the case of huge overdoses of either flurazepam or triazolam. Serious overdose can cause stupor or coma, but with rapid and appropriate medical treatment there is generally complete recovery. However, when an overdose of either drug is combined with other CNS depressants, such as alcohol or barbiturates, the probability of life-threatening complications is enhanced.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance develops more gradually to the sleep-inducing effects of flurazepam and triazolam than is the case with other sedative/hypnotic drugs when either of these substances is taken every night.[4] However, the degree to which the sedative/hypnotic benzodiazepines retain their effectiveness when taken for protracted periods has not been fully established.

Cross-tolerance occurs among the sedative/hypnotic benzodiazepines. Thus, once tolerance to the sleep-inducing effects of flurazepam at a given dose is developed, the user will also be tolerant to the dose of triazolam necessary to produce the same desired effect. Cross-tolerance also occurs between these drugs and the minor tranquillizer benzodiazepines (diazepam, oxazepam, chlordiazepoxide, etc.). Cross-tolerance is also reported to occur between the sedative/hypnotic benzodiazepines and such other sleep-inducing drugs as the barbiturates.

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[4] This is another advantage of these two drugs over most other sleep-inducing agents.

Psychological Dependence and Physical Dependence/Withdrawal

The incidence of psychological dependence on the sedative/hypnotic benzodiazepines is not known, although it is generally thought to be quite low. However, psychological dependence seems to develop in some long-term regular users; in such instances, it may be manifested both as an adamant unwillingness to discontinue the use of the drug even when the inherent psychoactive effects are diminished and as anxiety (or possibly feelings of panic) if the drug is temporarily unavailable.

The capacity of either flurazepam or triazolam to produce physical dependence when taken chronically at therapeutic dose levels has not been established; however, there have been a few cases of physical dependence on flurazepam involving patients believed to be taking excessively high nightly doses. In these cases, abrupt termination of use has led to a mild withdrawal sickness, appearing a few days after the last dose; withdrawal symptoms include anxiety, restlessness, depression, and sleep dysfunctions.

A period of mild rebound insomnia and other sleeping difficulties usually follows the abrupt termination of chronic nightly use of most sleeping pills, even when taken at therapeutic dose levels; some researchers believe that these symptoms, which may last for several days, constitute a form of physical withdrawal. The symptoms are fairly common among chronic users of triazolam but not of flurazepam. It is thought that in the case of flurazepam the rebound symptoms usually do not occur because its principal psychoactive metabolite, desalkylflurazepam, is gradually eliminated over several days, during which time the body can readjust to progressively lower concentrations.

PATTERNS OF USE

Flurazepam is by far the most widely prescribed sleeping pill. In the United States, it is estimated that 13 million prescriptions for flurazepam are written yearly. Among all psychoactive drugs, only diazepam and chlordiazepoxide are prescribed more frequently. The principal consumers are women and middle-aged and elderly patients. Flurazepam is rarely encountered among street drug users.

Information regarding the extent of use of triazolam in North America is not yet available, as this drug has only recently been introduced here. However, it has been widely used in Europe for several years.

ABUSE POTENTIAL

In contrast to all other sedative/hypnotic drugs, the sedative/hypnotic benzodiazepines do not produce euphoria and therefore have a very low dependence liability. They are also acknowledged to be much safer and to have a lower abuse potential.

Caffeine

DRUG CLASS: CNS STIMULANT

SYNOPSIS

Caffeine is the most widely and regularly consumed psychoactive substance in the world. When taken even in moderate amounts (such as one or two cups of brewed or percolated coffee), caffeine can produce elevated mood, increased alertness and respiratory rate, and a slight increase in blood pressure. If taken before bedtime, it can retard the onset of sleep. While low to moderate daily doses of caffeine do not appear to produce harmful effects in otherwise healthy adults, higher daily doses (such as six cups of coffee) can result in insomnia, nervousness, irritability, tremor, headache, and sometimes abnormally rapid and irregular heartbeat. Children are particularly susceptible to caffeine's adverse effects.

Because of its tendency to constrict cerebral blood vessels, caffeine is also used in combination with other drugs to combat migraine and other cerebrovascular headaches associated with high blood pressure. However, contrary to popular belief, caffeine is not effective in ameliorating headaches due to other causes, and in some cases it may even exacerbate pain. In other medical uses, caffeine is employed to counteract certain symptoms (such as respiratory depression) associated with CNS-depressant poisoning, and in the management of hyperkinetic syndrome in certain children.[1]

DRUG SOURCE

Caffeine is derived from any of several plants:

- seeds of *Coffea arabica* and related species (coffee);
- leaves of *Thea sinensis* (tea);
- seeds of *Theobroma cacao* (cocoa, chocolate);

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[1] For discussion of hyperkinetic syndrome see the Stimulants chapter in section 2.

- leaves of the South American maté plant *Ilex paraguariensis* (yerba maté);
- kola nuts from the tree *Cola acuminata* (cola drinks).

TRADE NAMES

There are few over-the-counter stimulant products exclusively containing caffeine available in Canada. However, the combination products Stimutabs and Wake Ups (tablets containing caffeine and theophylline)[2] and Alert (caffeine and dextrose) are available without prescription.

STREET NAMES

None in common use.

COMBINATION PRODUCTS

Apart from various beverages and chocolate, caffeine is a constituent of several analgesic products, most frequently combined with ASA, or ASA and codeine: Excedrin, 217, 217 MEP, 282 MEP, 222, 282, 292, 294, 293. (Excedrin, 217, and 222 may be obtained without prescription.)

Cafergot is a combination of caffeine and ergotamine.

MEDICAL USES

- in combination products, to treat cerebrovascular headache associated with hypertension;
- to treat headache associated with caffeine withdrawal (see below: Tolerance and Dependence);
- to counteract certain symptoms of CNS-depressant poisoning such as respiratory depression (now rarely);
- to control the symptoms of hyperkinesis in certain children; and
- to act as a mild stimulant for an assortment of medical problems.

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[2] Theophylline is also a stimulant chemically similar to caffeine.

PHYSICAL APPEARANCE

Caffeine, in its pure form, is a white crystalline powder resembling cornstarch in appearance.

DOSAGE

Medical

In headache medications, 30–100 mg. In over-the-counter stimulants, 100–250 mg.

Nonmedical

A medium-strength cup of percolated or brewed coffee would contain about 100 mg of caffeine; weak coffee might contain 40 mg per cup, and strong coffee up to 180 mg. Instant coffee would range between 30 and 100 mg, and decaffeinated coffee between 1 and 20 mg.

A medium-strength cup of tea would contain about 30 mg of caffeine, and the range according to strength would run from 10 to 90 mg.

Cola drinks vary from 20 to 45 mg of caffeine per 10-ounce can; the most common level is 30 mg.

A typical chocolate bar contains between 20 and 25 mg.

With coffee or tea, both method of preparation and amount used account for the variations in caffeine content. The various strains of the coffee plant—Colombian, Brazilian, Java, Jamaican, etc.—also differ in caffeine content.

ROUTES OF ADMINISTRATION

In medical uses, caffeine is a constituent in tablet and capsule products for oral consumption. It has also been administered (combined with sodium benzoate for solubility) by injection for its mild respiratory-stimulant properties.

Occasionally abusers have injected the drug intravenously.

EFFECTS OF SHORT-TERM USE: LOW DOSES[3]

CNS, behavioral, subjective: Mild mood elevation, heightened sensory awareness, increased alertness, and postponement of fatigue and drowsiness commonly occur. There is contradictory evidence regarding caffeine's effect on performance, and it would appear that the expectations of the individual play a significant role. While some researchers have reported that caffeine produces a more rapid and clear flow of thought, produces more sustained intellectual effort, and may lengthen the period during which one's best performance on motor tasks can be maintained, it has also been observed that caffeine does not appreciably shorten or improve reaction time and does not enhance, and may even impair, fine motor coordination.

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[3] One or two cups of medium-strength coffee: i.e., not more than 250 mg.

Although coffee is frequently given to alcohol-intoxicated persons, there is no evidence that caffeine has any other effects on them than to combat drowsiness.

When taken by abstainers, caffeine can produce nervousness and may cause a jittery feeling.

When taken shortly before bedtime, the following may also result:

- delayed onset of sleep and in some cases insomnia;
- diminished sleep time;
- reduced average depth of sleep; and
- increased early REM sleep (rapid eye movement sleep, when most dreaming occurs) but reduced later REM sleep.[4]

Cardiovascular: increased body temperature; constriction of the cerebral blood vessels (an effect which is believed to be responsible for relief from hypertensive headache); increased peripheral blood flow except in the brain; stimulation of cardiac muscles; and slightly increased blood pressure.

Respiratory: mild stimulation of respiration.

Gastrointestinal: gastric secretion stimulated by both caffeine and other components of coffee; inhibition of glucose metabolism, which can result in higher blood sugar levels; and increased free-fatty-acid levels.

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[4] For discussion of REM sleep, see the subsection Normal Sleep in the CNS Depressants chapter, section 2.

Other: relaxation of certain smooth muscles; increased urine flow.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[5]

Intensification of the low-dose effects may occur as well as any of the following effects:

CNS, behavioral, subjective: irritability, restlessness, nervousness, tremor; insomnia; and occasionally a mild form of delirium (manifested as imagined noises and flashes of light).

Cardiovascular: rapid and irregular heartbeat resulting from the direct effects of caffeine on the heart muscles, and increased blood pressure.

Other: has been reported as stimulating the synthesis and release of norepinephrine (also called noradrenalin) in the brain.

At very high doses (1,000–2,000 mg or higher), caffeine can produce highly abnormal cardiac rate and rhythm, extreme agitation, restlessness and tremors, a high blood sugar level, acid in the urine, and abnormally rapid reflexes. At potentially lethal doses, convulsions may also occur.

EFFECTS OF LONG-TERM USE

Daily use in low to moderate doses in otherwise healthy adults does not appear to produce any deleterious effects. However, substantial daily doses (i.e., 600 mg and over—the equivalent of six to eight cups of coffee) can lead to several adverse consequences. Among the most frequently observed symptoms are chronic insomnia and/or disturbed sleep, anxiety, restlessness, depression, gastrointestinal irritation, and abnormally rapid and irregular heartbeat.

In still higher daily doses (1,000 mg and over), a syndrome referred to as “caffeinism” has been reported (Penna, 1977). In many respects the symptoms are similar to anxiety neurosis: nervousness, irritability, agitation, headache, abnormally rapid breathing, tremulousness, and muscle twitches. Primary sensory disturbances are excessive sensitivity to pain, touch, or other stimuli and ringing in the ears. Chronic insomnia and/or delayed sleep with frequent awakenings also occur.

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[5] Single doses of several hundred milligrams or more, or lower doses in particularly sensitive individuals.

LETHALITY

Deaths resulting from severe overdose of caffeine are very rare. The lowest reported lethal dose was 3,200 mg, administered intravenously. Fatal single oral dose in adults is estimated to be approximately 10 grams (10,000 mg); this amount can result in convulsions and death due to respiratory arrest. Substantially lower doses can prove fatal to children.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance to caffeine's CNS-stimulant effect has not been clearly demonstrated. What little research has been reported suggests that caffeine before bedtime is less likely to produce insomnia in regular coffee drinkers than in abstainers. The ritual behavior regarding the almost mandatory cup of coffee with breakfast appears to indicate a strong psychological component in its habitual consumption. Even if tolerance does occur, the drinker's expectations of mild stimulation appear to outweigh it. For many, a single cup of coffee can retain its value as a "pick-me-up" for literally years; there does not appear to be a need to increase the amount in order to produce the same effects.

Psychological Dependence

The above factors point to the presence of mild psychological dependence: the daily coffee "habit" becomes necessary to produce a feeling of well-being and a readiness to pursue the day's activities. Many a coffee drinker would likely be somewhat distressed if the morning dose were not available. That taste and aroma play a substantial supporting role (as reinforcers) in psychological dependence on the caffeine in coffee is clearly demonstrated by the refusal of many to accept tea as a morning beverage in the absence of coffee.

Physical Dependence/Withdrawal

Most observers agree that physical dependence, albeit relatively mild, can result from chronic consumption of moderately high daily doses of caffeine—perhaps a half-dozen or more cups of coffee per day. The most characteristic symptom of withdrawal sickness upon abrupt termination of use is severe headache which can rapidly be relieved by a cup of coffee or a caffeine tablet. Other relatively common symptoms include irritability, lethargy, nervousness, restlessness, and reduced efficiency.

PATTERNS OF USE

Caffeine is the most widely used psychoactive substance in the world. However, recent extreme escalations in the cost of coffee, tea, and chocolate appear to be bringing about a decline in sales.

Prior to the 1975 price increases, Canadians averaged 4.1 kilograms per capita of imported unroasted coffee beans per year—sufficient for slightly more than two cups per day for every person over the age of 14. In the United States and many European countries, 1975 average coffee consumption rates (based on import figures) ranged as high as three to six cups per day. Tea consumption rates per capita in Canada were similar to coffee—approximately two cups per day for each adult. By comparison, Americans averaged less than one cup of tea per day.

Pre-1975 surveys suggest that approximately 5% of adults in Canada consumed caffeine in daily amounts equivalent to seven cups of coffee, a dose level which may lead to the onset of such unpleasant side effects as reported above.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of caffeine is moderately low, mainly because of the mildness of its stimulating and mood-elevating properties and its typical route of administration. Because caffeine products are orally consumed, the time period for reaching the target sites in the brain is greater than for injection routes of administration; therefore, primary gratification is delayed.

Inherent Harmfulness

Low to moderate daily doses of caffeine are well tolerated by most adults, although for some even one or two cups of coffee in a day can produce a state of nervousness and tension. At higher doses (six to eight cups of coffee per day) a number of unpleasant side effects occur, such as irritability, tremor, insomnia, and rapid and irregular heartbeat. These tend to restrict regular high-dose abuse.

Availability

When the factor of availability is considered, the abuse potential of caffeine is relatively high, for caffeine-containing beverages and foods are readily available and enjoy a high degree of social acceptability. Moreover, most regular users are willing to accept whatever deficits may result from coffee or tea drinking because of the attendant feelings of enhanced well-being and alertness.

REFERENCE

Penna, R.P. (project director), *Handbook of Non-Prescription Drugs*, 5th ed., American Pharmaceutical Association, Washington, D.C., 1977.

Cannabis

(Marijuana, Hashish, Hashish Oil)

DRUG CLASS: HALLUCINOGEN

SYNOPSIS

Marijuana, hashish, and hashish oil are obtained from the plant *Cannabis sativa*, a hardy annual which grows in both tropical and temperate climates. The principal psychoactive constituent in this plant is tetrahydrocannabinol (THC),[1] a hallucinogenic substance that is mild when compared by weight to LSD. The concentration of THC in marijuana usually ranges up to approximately 8% of the bulk weight for leaf products sold on the street in North America, while the concentrations in resin preparations (hashish and hashish oil) range up to 15% and 60% respectively. Actual street concentrations, however, are usually lower, varying widely according to source of supply.

At low to moderate doses, cannabis usually induces a general feeling of well-being, relaxation, and emotional disinhibition. A wide spectrum of perceptual and sensory distortions may be experienced, although at these dose levels the effects are not nearly so intense as those associated with LSD. Mild cognitive and motor impairment typically occurs during cannabis-taking episodes; other very common physiological effects involve the cardiovascular system—increased heart rate and pulse rate, as well as a small drop in blood pressure.

At the very high dose levels normally associated with the use of hashish oil, the effects of cannabis can more closely approximate those of LSD in kind and in intensity, and the probability of adverse psychological reactions increases. True hallucinations can occur and may be accompanied by disorganized thought, paranoia, and panic. Fortunately, such severe reactions are infrequent among normal users; since the effects of smoked cannabis are rapidly experienced, users are

[1] Tetrahydrocannabinol exists in *Cannabis sativa* in several chemical forms. The main psychoactive constituent is Δ^9-tetrahydrocannabinol (also called Δ^1-tetrahydrocannabinol).

able to discontinue their intake before adverse effects become too serious.

Tolerance develops to the desired psychoactive effects of cannabis with regular use, and regular use may also cause psychological and mild physical dependence. Abrupt abstinence after protracted and regular high-dose use can result in a withdrawal syndrome which includes sleep disturbances, anxiety, restlessness, sweating, loss of appetite, and upset stomach.

The effects of chronic daily or almost daily use have recently become the subject of extensive research. Most findings are preliminary (and sometimes contradictory). However, there is a growing body of evidence that chronic heavy cannabis smoking is particularly harmful to the body's respiratory system.

Although survey evidence in North America indicates that cannabis is the illegal psychoactive drug most widely used (with the exception of alcohol and tobacco used by minors), most evidence suggests that the vast majority of North Americans have never used cannabis, and most of those who have used it have done so infrequently and experimentally.

DRUG SOURCE

Cannabis sativa, the botanical name for the Indian hemp plant, is an annual from which marijuana, hashish, and hashish oil are prepared. More than 60 constituents, known as cannabinoids, occur naturally only in the cannabis plant. The principal psychoactive cannabinoid is tetrahydrocannabinol (THC). *Cannabis sativa* readily grows in both tropical and temperate zones, and there are numerous cultivated and naturally occurring strains (varying in hallucinogenic potency) found throughout the world.[2] Frequently, cannabis is bought and sold on the street under names associated (often incorrectly) with the geographical origin of the cannabis preparation: Colombian, Acapulco Gold, Jamaican, Mexican, Panamanian, etc.

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[2] *Cannabis sativa* is a species of plant generally considered to exist in several varieties; therefore, reference is often made to *Cannabis sativa* var. indica and *Cannabis sativa* var. ruderalis as particular varieties within the *Cannabis sativa* species. However, during the 1970s the view was held by some botanists that these "varieties" were actually cannabis species different from *Cannabis sativa*—i.e., that *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis* were three different species of cannabis.

TRADE NAMES

There is no generally accepted medical use for cannabis. When used in research, cannabis preparations and individual cannabinoids are usually referred to by a botanical or chemical name respectively.

STREET NAMES

Few psychoactive drugs have as many street names as does marijuana. The name "marijuana" is likely derived from the Mexican slang for any cheap tobacco; one street name is the English equivalent, Mary Jane. Some of the more commonly applied colloquialisms are: Acapulco Gold, ace, bhang, Colombian, ganja, grass, hemp, Indian, Jamaican, jive (sticks), joint, Mexican, Panama Red, Panama Gold, pot, reefer, ragweed (low-grade marijuana), sativa, tea, Thai sticks, weed. "Roach" refers to the remainder of a marijuana cigarette after most has been smoked. A "roach clip" (which may be an ornamental commercial product or simply a bobby pin) holds the small remainder until virtually all has been consumed.

The derivation of the name hashish may be from the Arabic for "dry grass"—or, more colorfully, from Hasan-ibn-al-Sabbah, the founder of the 11th-century Assassins. According to legend, ritual murders were carried out by the Assassins after they had achieved hashish intoxication.[3] The only widely used street name is "hash," although there are many geographically local terms.

The viscous, highly potent oil of cannabis resin is most frequently referred to as "hash oil" or "honey oil." Oil derived from leaf material is called "weed oil."

DRUG COMBINATIONS

- cannabis and PCP, referred to as "supergrass" or "angel dust";
- cannabis and opium, referred to as "O.J." (i.e., opium joint);
- cannabis and heroin, referred to as "atom bomb" or "A-bomb."

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[3] However, it is now thought that they were provided with hashish, women, etc., and then told that the continuing provision of their pleasures was contingent upon their performing the murders.

MEDICAL USES

There are no generally accepted medical uses. However, marijuana, THC, and structurally similar synthetic chemicals are currently under study in the treatment of epilepsy, wide-angle glaucoma, anorexia nervosa, asthma, and severe pain, and for relief of nausea and vomiting produced by anticancer therapy. (See nabilone, section 5.)

PHYSICAL APPEARANCE

The plant *Cannabis sativa* can grow to heights of 4.6 meters (15 ft), although most strains grown in North America are considerably shorter. Both male and female forms of the cannabis plant occur (i.e., it is dioecious). Both sexes have large leaves (consisting of 5 to 11 leaflets with serrated margins) which are deep green on the upper side and light green on the lower. The female plant secretes a sticky resin which covers the flowering tops and upper leaves.

Marijuana is prepared from the dried flowering top and leaves of the harvested plant. The THC concentration in the resulting marijuana depends upon both the genetic characteristics of the plant and the proportions of flowering parts, upper leaves, lower leaves, stems, and seeds present in the marijuana preparation.[4] Marijuana may range in color from grayish-green to greenish-brown, depending on where it was grown, and in texture from a dry powder to a dry leafy material to a finely divided tealike substance. Occasionally, materials such as tea or tobacco are added to dilute the marijuana before it is offered for sale on the street.

Hashish consists of dried cannabis resin and compressed flowers, and ranges in color from light ocher brown to almost black. It is usually available on the street in the forms of hard chunks or cubes.

The viscous, highly potent oil of cannabis is obtained by extracting the cannabinoids, including THC, from hashish (or, less often, marijuana) with an organic solvent, concentrating the filtered extract, and in some cases subjecting it to further purification. The color may range from clear to almost black.

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[4] For a given plant, the THC concentration is usually greatest in the bracts (the small leaves at the base of the flowers) and decreases from the flowering tops to upper leaves to small stems to large stems to seeds to roots. If the female plant is kept unfertilized (i.e., by killing the male plant before pollen is produced), it will flower more abundantly and thereby produce more resin (and THC). Marijuana so cultivated is called *sinsemilla* (literally, "without seeds").

DOSAGE

Medical

At present, there is no official clinical use for this drug. In experimental studies in which THC is administered in capsules, dosages have ranged up to 20 mg.

Nonmedical

A "joint" of marijuana the size of a cigarette typically contains between 2.5 and 5.0 mg of THC. Street purchases from unreliable sources may contain even less.

A very small amount of cannabis (e.g., containing 1 mg of THC) can produce a pleasurable high for the occasional user, and a single typical "joint" may be sufficient for two or three nontolerant smokers. A heavy regular smoker may consume five or more "joints" per day.

ROUTES OF ADMINISTRATION

Almost all possible routes of administration have been used, but by far the most common method is smoking (inhaling) a hand-rolled "joint" resembling a cigarette (usually with the ends twisted or folded). Smokers inhale deeply, and then hold their breath for several seconds in order to ensure maximum absorption of the THC by the lungs. Both marijuana and hashish are also frequently smoked through a pipe, and various types of pipes are available for just that purpose (some quite exotic in appearance). Oil of hashish is used sparingly because of its extremely high psychoactive potency; often a single drop is applied to a "joint," a cigarette, or another smokable substance. Very heavy users, however, may use as much as a gram of this potent product per day.

Crude extracts of cannabis have on occasion been injected. This route is rarely used, however, because of the very unpleasant side effects such as severe pain and inflammation at the site of injection. (A variety of toxic systemic effects have also been reported.) Cannabis, particularly hashish, may be cooked or baked in foods and eaten. In clinical research, THC is usually prepared in gelatin capsules and administered orally. The oral dose must be three to five times greater than the smoked dose to produce equivalent effects.

EFFECTS OF SHORT-TERM USE: LOW TO MODERATE DOSES[5]

CNS, behavioral, subjective:

1. Early effects include disinhibition and garrulousness. Many users also experience relaxation and drowsiness; by contrast, many other hallucinogens, such as LSD, initially induce a state of arousal.
2. The user usually experiences a general feeling of well-being, which can be manifested as exhilaration and euphoria.
3. Distortions of the perception of time, body image, and distance frequently occur; users may also experience increased auditory and visual acuity and thus may perceive ordinary objects as taking on magnified importance.
4. Tactile, olfactory, kinesthetic, and gustatory senses are often enhanced.
5. Spontaneous laughter very commonly occurs.
6. There may be mild impairment of recent memory and concentration as well as mild confusion and disorientation.
7. Attention span may be reduced and the user's ability to process information may be impaired.
8. Balance and stability when standing can be impaired, and the user tends to experience decreased muscle strength and hand steadiness; slight tremor may also occur.
9. There can be impaired ability to perform complex motor tasks (e.g., in simulated driving tests).
10. Some users experience such adverse reactions as fearfulness, anxiety, or even panic, as well as mild paranoia. However, at relatively low dose levels abusive or violent behavior influenced by cannabis is rare.

Cardiovascular: increased heart rate; increased peripheral blood flow; slight drop in body temperature and blood pressure, particularly when moving from a sitting to a standing position; reddening of the eyes.

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[5] Doses of 5 mg of THC or less (the equivalent of one marijuana cigarette) smoked by nontolerant users.

Respiratory: irritation of the mucosal membranes lining the respiratory system; bronchodilation.

Gastrointestinal: increased appetite; dryness of the mouth and throat.

Other: changes in libido. Headache and "hangover" may occur when effects begin to wear off.

The intoxication produced by a single "joint" may last for two to three hours. If cannabis is taken orally (swallowed), the effects may last for up to 24 hours.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[6]

Intensification of the low-dose effects may occur as well as any of the following effects:

CNS, behavioral, subjective: Synesthesias may occur—that is, the melding of one sensory modality with another so that, for example, music is "seen." Pseudohallucinations occasionally occur—that is, hallucinations which are known to the user to be unreal. The probability of adverse psychological consequences tends to increase as the size of the dose increases. Judgment is impaired; reaction time is slowed; performance in simple motor tasks is impaired. There may be confusion of past, present, and future. True hallucinations may occur, as well as delusions and feelings of depersonalization (i.e., the belief that one is "unreal"). Thoughts are increasingly confused and disorganized; pronounced paranoia, agitation, and panicky feelings may replace early euphoria; sometimes the user fears that the drug-induced state will never end.

At very high doses, some users experience an acute toxic psychosis characterized by hallucinations, paranoid delusions, disorientation, intense feelings of depersonalization, severe agitation, and loss of insight. The use of cannabis may also unmask latent schizophrenia, a condition which may continue to be experienced indefinitely.

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[6] Doses of 10–20 mg of THC or more smoked by nontolerant users, or lower doses in particularly sensitive individuals.

EFFECTS OF LONG-TERM USE

Psychological Effects

The occasional low-dose use of cannabis does not appear to produce harmful psychological effects in healthy adults; furthermore, more regular low-dose use (i.e., smoking a single marijuana cigarette or less one or two times a week) probably does not significantly affect normal psychological functioning in healthy adults, although very mild psychological dependence may develop. The risk of more pronounced psychological dependence is particularly high among users with emotional problems who turn to cannabis for relief from psychological stress. They may come to depend inappropriately on cannabis instead of learning drug-free means of coping with stress.

Very regular high-dose use of cannabis may cause significant psychological adjustment problems in some users. The degree and type of maladjustment is the subject of disagreement among researchers. One pattern of behavior, often referred to as the amotivational syndrome, has been reported to be manifested in some chronic heavy users of cannabis and/or LSD. The characteristics of this syndrome are described in the following passage:

> . . . personality changes that seem to grow subtly over long periods of time: diminished drive, lessened ambition, decreased motivation, apathy, shortened attention span, distractibility, poor judgment, impaired communication skills, loss of effectiveness, introversion, magical thinking, derealization and depersonalization, diminished capacity to carry out complex plans or prepare realistically for the future, a peculiar fragmentation in the flow of thoughts, habit deterioration and progressive loss of insight. (West, 1970, p. 328)

The described symptoms of the amotivational syndrome are quite similar to many of the attributes of the lifestyle adopted by many young people during the 1960s and early 1970s—for example, "diminished drive," "lessened ambition," "decreased motivation," "peculiar fragmentation in the flow of thoughts," and "diminished capacity to . . . prepare realistically for the future." The lifestyle was often ascribed to "hippies" and other fringe members of society, some of whom were indeed very heavy users of marijuana. However, it is difficult to determine whether it is the lifestyle, the drug use, or a combination of the two that is the source of the symptoms. Evidence of a causal relationship between the heavy use of cannabis (and other drugs) and the development of the amotivational syndrome cannot be demonstrated from the limited clinical evidence now available.

Conservatively, it may be suggested that heavy use of cannabis (and other drugs) may serve to foster the amotivational syndrome in some users, while, conversely, certain aspects of the amotivational syndrome may serve to foster the heavy use of cannabis (and other drugs) in others. In many cases, it is likely that the amotivational syndrome arises from the combination of both causes: a preexisting disposition to the symptoms described, reinforced by chronic heavy use of cannabis.

There are certain symptoms which fairly commonly occur in chronic heavy cannabis users, the most important of which are memory and concentration impairment. These symptoms tend to clear after a few weeks of abstinence, although persistent dysfunction has been described in a few instances after abstinence has been established. To date the question of whether permanent brain tissue damage in humans arises from chronic heavy use of cannabis has not been settled.

Other Adverse Effects

One organ system which does appear to be particularly affected by chronic heavy cannabis smoking is the respiratory system. Bronchitis, asthma, sore throat, and chronic irritation of and damage to the sensitive mucosal membranes lining the respiratory tract are conditions generally acknowledged to have a much higher incidence among heavy smokers of cannabis than among occasional users and nonusers.

These problems should not be surprising, for cannabis, when smoked, yields substantially more tar than strong brands of tobacco, and the tar from cannabis possesses a higher concentration of certain cancer-producing agents (e.g., benz[a]pyrene) than that from tobacco smoke.[7] A greater percentage (by weight) of the available benz[a]pyrene in smoked cannabis is retained by the lungs than is the case with smoked tobacco, for the cannabis smoker generally inhales more deeply and typically holds cannabis smoke in the lungs for much longer periods per puff. The prolonged holding of cannabis smoke ensures maximum absorption of its desired psychoactive constituents; however, this practice may increase the risk of lung cancer for heavy regular smokers of cannabis, particularly if they are also heavy cigarette smokers.

Other Areas of Investigation

1. The long-term effects of chronic cannabis smoking on the car-

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[7] Tar is the residue of tiny particles produced by the combustion of cannabis or tobacco.

diovascular functions do not appear to be significant in users without a history of heart disease or other cardiovascular disorder.

2. The findings on the long-term effects of cannabis use on sexual functioning in human males are not uniform; however, most current evidence suggests that there is no substantial effect on fertility. There has been practically no research on the effects of long-term cannabis use on human female sexuality. Claims of possible genetic or congenital abnormalities arising in the children of chronic heavy cannabis smokers are premature, as longitudinal studies of the children have not yet been carried out. The resolution of this issue is likely to be confounded by the fact that most cannabis users also use other drugs.
3. There is some evidence that chronic heavy use of cannabis may adversely affect certain components of the body's immune system. However, findings are not uniform, and epidemiological studies in this area are necessary before any conclusions can be drawn.

LETHALITY

There have been no reports of deaths in human beings directly attributable to cannabis overdose. However, it is very likely that a number of deaths have resulted indirectly: for example, cannabis has probably contributed to at least some fatal auto accidents, for it has adverse effects on such important driving skills as judgment, perceptual/motor coordination, ability to concentrate, and depth perception.

TOLERANCE AND DEPENDENCE

Tolerance

Over a short period of everyday use (e.g., a few consecutive days), a form of "reverse tolerance" to the effects of cannabis can occur; in such cases, the user experiences the psychoactive effects more readily and with smaller amounts of the drug on the second and subsequent occasions than on the first occasion. Several possible nonpharmacological explanations have been offered for this phenomenon. One suggestion is that the user learns the appropriate smoking technique and develops a more relaxed "set" (i.e., more favorable expectations and attitudes). However, in research experiments involving frequent and longer-term regular administration of high daily doses of cannabis, users acquire tolerance to the desired effects; clinical observations of chronic heavy cannabis users support the research finding. Therefore, if very regular high-dose smokers wish to maintain the desired intensity of initial psychoactive effects, they must increase their daily dose; abstinence for at least several days can restore original sensitivity.

Tolerance develops to several other effects of cannabis after very regular high-dose use: to the rapid heart rate, to other mild adverse cardiovascular effects, to impairment of performance on psychomotor tasks, and to other forms of cognitive impairment. Daily low-dose use of cannabis may in some users not result in any appreciable acquisition of tolerance to the desired effects, although tolerance to impairment of psychomotor functioning does occur with a resultant improvement in task performance; also the acceleration of heart rate is somewhat reduced with chronic daily low-dose use.

There is no evidence that cross-tolerance develops between cannabis and other hallucinogens. (Cross-tolerance does develop among LSD, mescaline, and psilocybin.)

Psychological Dependence and Physical Dependence/Withdrawal

With regular use, psychological dependence on cannabis can develop. Users acquire a persistent craving for its psychoactive effects and the drug consequently takes on a central role in their life. If cannabis is temporarily unavailable, anxiety or even feelings of panic may ensue.

Physical dependence on cannabis may develop in those who daily use high doses; abrupt termination of use can produce a mild withdrawal syndrome, with symptoms including sleep disturbance, irritability, loss of appetite and consequent weight loss, nervousness, anxiety, sweating, and upset stomach. Sometimes chills, increased body temperature, and tremors occur. The withdrawal sickness usually lasts for less than a week.

PATTERNS OF USE

Surveys of drug use among Ontario students (grades 7–13) taken in 1977 and again in 1981 indicate that during this period there was a statistically significant increase in the number of young people who reported having used cannabis at least once during the 12 months preceding each survey; the increase in users moved from 25% of all students in 1977 to 30% in 1981.[8] These surveys found that the incidence of cannabis use ranked third among all drugs of abuse, behind alcohol and tobacco. Furthermore, the 1981 survey found that use increased with age: approximately 40% of those students 16 years old and over had used cannabis at least once during the previous year.[9]

A 1979 nationwide Canadian survey of cannabis use among adults (Rootman, 1979) found that almost 10% of respondents acknowledged some use of cannabis during the 12 months prior to the survey; this rate is substantially lower than the rate for Ontario high school students. Furthermore, only 4% of adults surveyed reported regular use of cannabis.[10] Directly comparable figures were not reported for the Ontario high school students,[11] but American survey data of young people indicate regular cannabis use at a substantially higher rate than 4%.

The Ontario and the Canada-wide surveys reflect regional, age, sex, and socioeconomic differences among cannabis users. The overall figures are not substantially dissimilar to those reported for most other Western countries, which also show a trend throughout the 1970s toward a per capita increase in the use of cannabis, although 1980 and 1981 survey data seem to reflect a leveling off, and in some instances a slight decline.

A key factor in the much higher rate of occasional use of cannabis among students as compared to adults is that the large majority of youthful users are experimenters: that is, most young users try cannabis on only a few occasions and then discontinue. It is possible that after having satisfied their curiosity they lose interest, or that after having bowed to peer-group pressure to try it out, they are then relieved of further pressure to use it. Support for the experimentation hypothesis is found in the Canadian adult study: while 17.2% of respondents had used cannabis at some time in their lives, only 9.7% of these same people had used it within the past 12 months.

[8] Peak use was recorded in 1979, when 32% of all students reported cannabis use at least once in the preceding 12 months.

[9] Also a drop, from almost 50% of all students 16 and older sampled in the 1979 Ontario survey.

[10] "Regular use" in the adult survey was defined as more than once a week during the past 30 days.

[11] The 1981 Ontario high school survey found that approximately 14% of all students reported use of cannabis at least 10 times during the past 12 months.

ABUSE POTENTIAL

Dependence Liability

The euphoria ("high") produced by cannabis is generally not as intense as that produced by those drugs with a high dependence liability, such as cocaine or heroin. In fact, many users claim they take cannabis because of the mellow and relaxing state it tends to create. These pleasurable effects do not appear to be sufficiently great to induce serious dependence problems in most users.

Inherent Harmfulness

It is generally acknowledged that occasional use of cannabis is not ordinarily harmful to healthy adults. For those who heavily and regularly abuse it, the quick gratification obtained from cannabis smoking apparently greatly outweighs any concern they may have over possible long-term harmful consequences.

Availability

Most cannabis users, including young people, are normally able to obtain the drug through illicit means without great difficulty. Furthermore, compared to many other illicit drugs, cannabis is relatively inexpensive. Both factors contribute to the widespread abuse of cannabis in North America.

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Cocaine

DRUG CLASS: CNS STIMULANT;
LOCAL ANESTHETIC

SYNOPSIS

Cocaine is a powerful central nervous system (CNS) stimulant which produces heightened alertness, inhibition of appetite and need for sleep, and intense feelings of euphoria. It is prepared from the leaf of the coca bush found primarily in Peru and Bolivia. Originally isolated in Europe in the 1860s, it was introduced as a tonic/elixir in patent medicines to treat a spectrum of real or imagined maladies. Later it was found to be useful as a local anesthetic for eye, ear, and throat surgery, and it still continues to have certain limited surgical applications. Currently, it has no other clinical use, having been largely replaced by other synthetic local anesthetics such as lidocaine.

Because of its very potent euphoric and energy-increasing properties, cocaine was abused by many in the latter part of the 19th century, even though its extremely high dependence liability was recognized by some physicians. Around the turn of the century, legislation was introduced to restrict drastically its use in both Europe and North America. However, because of its highly prized effects, it remains an enduringly popular illicit drug of abuse.

DRUG SOURCE

Cocaine is prepared from the leaves of the *Erythroxylon coca* tree of Peru and Bolivia.

TRADE NAMES

Not applicable.

STREET NAMES

"C", coke, flake, snow, stardust.

COMBINATION PRODUCTS

Cocaine plus heroin is called "dynamite," "speedball", or "whizbang." Cocaine plus morphine is also called "whizbang."

MEDICAL USES

Formerly used as a local anesthetic for eye, nose, and throat surgery; currently used only rarely for topical anesthesia of the upper respiratory tract.

PHYSICAL APPEARANCE

Cocaine hydrochloride is an odorless white crystalline powder with a bitter numbing taste, very soluble in water and soluble in alcohol.

Street cocaine is often adulterated with such related (but nonpsychoactive) substances as lidocaine or benzocaine, both of which, when sniffed, produce a numbing effect in the nasal passages similar to that of cocaine. Other adulterants may mimic the taste or appearance of cocaine, and still others (e.g., caffeine) produce mild stimulating effects. Users sometimes attempt to remove these impurities and enhance the effects of cocaine by a chemical manipulation ("free basing") that includes extraction with appropriate solvents. Since some of these solvents are highly inflammable, the procedure can be dangerous.

DOSAGE

Medical

Solutions employed clinically for surface anesthesia vary from 10 mg/ml to 200 mg/ml.

Nonmedical

Very heavy users may sniff up to 10 pure grams (10,000 mg) per day, although most users take substantially less. A common pattern among users in social settings involves sniffing into each nostril 20–30 mg of cocaine. (These units are referred to as "lines.") Administration may be repeated two or three times an hour over several hours.

ROUTES OF ADMINISTRATION

Inhalation, sniffing ("snorting"), or injection (subcutaneous, intramuscular, and intravenous).

EFFECTS OF SHORT-TERM USE: LOW DOSES[1]

While the effects of cocaine are very similar to those of amphetamines, it has been reported that the naive user may experience very little during the first few occasions when the drug is taken. Some users have to learn to appreciate the CNS-stimulant effects of cocaine; the desired effects are more easily perceived with amphetamines. Effects which may occur are:

CNS, behavioral, subjective: pupillary dilation; increased reflexes; euphoria, a sense of well-being, postponement of physical and mental fatigue, inhibition of appetite and of need for sleep; increased garrulousness or quiet contemplation and rapture; elevated self-confidence and feelings of mastery over the environment or paradoxically anxiety or even panic; increased speed of performance on fairly simple physical and intellectual tasks (but the ability to perform more complex functions is not enhanced) or reduced effectiveness if the drug induces anxiety or overestimation of one's abilities.

Cardiovascular: constriction of the blood vessels, increase in heart rate after initial slowing, and increased blood pressure.

Respiratory: increased respiratory rate.

Gastrointestinal: dry mouth.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[2]

Intensification of the low-dose effects may occur as well as any of the following effects:

CNS, behavioral, subjective: When cocaine is injected intravenously, experienced users cannot initially discriminate between cocaine and methamphetamine in terms of euphoric effect. However, cocaine's effects diminish usually within 30–40 minutes, whereas those of methamphetamine may last for hours. Other effects may include tremors, vertigo, possibly severe agitation, increased spinal cord reflexes, muscle twitches, paranoid symptoms, and, with repeated and uninterrupted administrations, a toxic psychosis clinically indistinguishable from amphetamine psychosis.

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[1] Single doses up to approximately 20 mg.

[2] Doses of several hundred milligrams or more, or lower doses in particularly sensitive individuals.

Cardiovascular: headache, pallor, cold sweat, and rapid weak pulse.

Gastrointestinal: nausea and vomiting.

Hazardous dose levels may cause rapid, irregular, and shallow respiration, convulsions, and coma.

COCAINE "SPREE"

Cocaine users have reportedly taken the drug in large amounts in excess of several grams over a period of several hours. Such "sprees" are in many respects similar to the "run" in which amphetamine abusers indulge, but the "spree" covers a considerably shorter period of time. Toxic psychosis may occur and in most instances disappears when the drug is metabolized. Nevertheless, it may persist if the user attempts to counteract the unpleasant feelings associated with the "crash" by using more of the drug. The cocaine "crash" tends to be milder than that following the amphetamine "run."

EFFECTS OF LONG-TERM USE

Although the effects of chronic cocaine use have not been fully researched, some reliable observations have been reported. Nervousness, excitability, agitation, and paranoid thinking commonly occur, as do hypersensitivity (particularly to noises), mood swings, memory disturbance, insomnia, and impotence. Heightened reflexes along with muscle twitching and increased pulse rate may also result. Confusion and exhaustion, in reaction to extended periods of insomnia, are not unusual. Loss of appetite is also common.

Physical complications depend in part on the characteristic effects of this drug and in part on the mode of administration. If the drug is sniffed, constriction of the blood vessels in the lining of the nose eventually may lead to local destruction of tissue and may result in perforation of the nasal septum.

LETHALITY

Although cocaine and amphetamines do not chemically resemble each other, their pharmacological actions are remarkably similar. Death by overdose from either cocaine or amphetamines is indeed rare when compared to deaths by overdose from opiates or barbiturates. However, the death rate from accidents, suicides, and homicides is higher among heavy users of amphetamines than among the general population. Whether the same is true among heavy users of cocaine has not been documented.

In lethal doses delirium and rapid, irregular, and shallow respiration, convulsions, and unconsciousness precede death. Death usually results from depression of vital brain centres which control respiration, leading to respiratory arrest. When a lethally large dose is used intravenously, immediate death from cardiac arrest may result from a direct toxic action of cocaine on the heart.

Single doses of less than 1.2 pure grams (1,200 mg) have resulted in death, while in other cases an overdose in excess of 20 pure grams has not proved fatal.

TOLERANCE AND DEPENDENCE

Tolerance to the stimulant effect of cocaine has not been demonstrated in humans. Users may consistently employ the same dose level over an extended period without reporting a decline in the subjectively pleasurable effects of the drug. However, many users frequently increase their daily intake (amounts of up to 10 pure grams per day have been reported), presumably to intensify and prolong the effects produced by the drug. A reverse tolerance (that is, an increased sensitivity with repeated use) to cocaine's anesthetic and convulsant properties has been reported in humans.

Physical dependence does seem to occur, although not all researchers agree that the characteristic symptoms that accompany abstinence after regular use actually reflect physical dependence. However, the symptoms appear to be qualitatively similar to those following abstinence from other CNS stimulants, albeit considerably less pronounced than in the case of amphetamine withdrawal. Exhaustion, psychic depression, extended but restless sleep with increased REM (rapid eye movement) activity, and hunger upon awakening commonly occur after abrupt termination of use. The severity of the symptoms is partially dependent upon the length of a "spree" and the amount of the drug used.

Intense psychological dependence—a persistent craving for the psychological effects—can occur. It has also been reported that some cocaine users will remain moderately to severely depressed over extended periods of time when the drug is not available to them, and they remain preoccupied to the point of obsession with obtaining the drug. The depression immediately lifts upon administration of cocaine.

PATTERNS OF USE

There is considerable folklore and sensational press coverage devoted to cocaine use. Many people think of cocaine as a narcotic, and some governments legally classify it as such, even though it is pharmacologically quite different. Penalties for possession and trafficking in cocaine are among the most severe for any of the illegal drugs of abuse. Part of the cocaine mystique is its repeated association with the glamour professions—entertainment, music, and sports. Irrespective of whether that association is valid, cocaine is very expensive when compared to other illicit drugs, and its use is limited to the affluent. A drug with such a glamorous aura that receives so much publicity is likely to seem very attractive to some young people; however, the extent to which they use it is not known. The occasional user or experimenter who attempts to purchase the drug on the street may unwittingly be sold another drug with stimulant properties, such as amphetamines or more likely weaker stimulants.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of cocaine is among the highest for all drugs of abuse because of two key variables. First, the euphoria produced by cocaine is powerful. Second, since cocaine is highly soluble in water, large amounts can be dissolved and administered by injection directly into the bloodstream; intravenous administration in high doses permits both very rapid and intense gratification.[3]

Inherent Harmfulness

Inherent harmfulness is not usually a significant factor restricting cocaine's potential for abuse. Nevertheless, even at moderate doses, long-term intranasal administration can lead to local tissue destruction and possible perforation of the nasal septum.

However, as noted earlier, many experienced abusers occasionally administer cocaine repeatedly over several hours in very high doses either intravenously or intranasally; they are generally aware of the heightened risks attendant on such use and are also willing to accept them.

Availability

Cocaine is illegally exported from South America to North American markets. Law enforcement agencies vigorously pursue smugglers and others, meting out stiff penalties to those engaged in trafficking (or even those possessing cocaine for personal use). For these reasons, as well as the relatively high cost of production, the price of cocaine is usually very high. Its use is thus principally restricted to those who can afford the luxury cost.

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[3] Intense gratification also occurs very rapidly after intranasal administration ("snorting").

Codeine

DRUG CLASS: NARCOTIC ANALGESIC; OPIATE

SYNOPSIS

Codeine is a naturally occurring substance of the opium poppy, *Papaver somniferum.* Its euphoric and analgesic effects are mild; its clinical uses are in the management of mild to moderate pain and the control of cough. Tolerance to the main effects of codeine tends to develop gradually, and physical dependence on it occurs infrequently. However, a definite withdrawal syndrome can occur after chronic high-dose abuse (i.e., daily doses in excess of the therapeutic range); its symptoms are similar to but less intense than those occurring during withdrawal from morphine.

Because of the mildness of its effects and its potentially dangerous side effects at high doses (e.g., seizures), codeine is rarely the drug of choice for experienced abusers of narcotic analgesics. Codeine can be obtained in Canada and the U.S. without prescription under certain restricted conditions (for example, there are small amounts per unit dose in certain drug combination products); at such dose levels, however, it is unlikely to attract significant abuse.

DRUG SOURCE

Codeine is isolated from crude opium, the resinous preparation of the opium poppy, *Papaver somniferum.*

TRADE NAMES

Paveral syrup. Codeine phosphate is also marketed by several pharmaceutical firms under its generic name.

STREET NAME

Schoolboy.

COMBINATION PRODUCTS

- 222, 282, 292, 293, 294 (codeine phosphate, ASA, and caffeine citrate);
- Veganin (codeine phosphate, ASA, and caffeine citrate);
- Benylin syrup with codeine (codeine phosphate, diphenhydramine, and ammonium chloride);
- Sinutab with codeine (codeine phosphate, acetaminophen, phenyltoloxamin citrate, and phenylpropanolamine hydrochloride);
- elixir of terpin hydrate with codeine;
- "loads" (glutethimide plus codeine).

Veganin and 222, both containing codeine, are examples of Canadian analgesics which can be sold without prescription. Such products must contain two or more active non-narcotic drugs in combination with a maximum of 8 mg codeine per unit dose. Canadian cough syrups containing codeine, such as Benylin, can be obtained without prescription in combination products containing non-narcotic drugs provided the maximum amount of codeine does not exceed 3.8 mg per 5 ml.

MEDICAL USES

- suppression of cough reflex;
- relief of mild to moderate pain.

PHYSICAL APPEARANCE

Codeine phosphate is an odorless, white crystalline powder freely soluble in water and slightly soluble in alcohol.

DOSAGE

Medical

- for suppression of cough—5 to 10 mg taken orally every three to four hours;
- for relief of mild to moderate pain (not adequately relieved by

non-narcotic analgesics such as ASA)—30 to 60 mg taken orally or by injection every three to four hours.

Nonmedical

Daily doses of up to 1,800 mg have been reported; however, codeine abusers ordinarily administer substantially less of the drug because of the potentially serious side effects which can occur at very high doses.

ROUTES OF ADMINISTRATION

Orally or by subcutaneous or intramuscular injection.[1]

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, behavioral, subjective: suppression of the sensation of mild to moderate pain;[3] suppression of cough reflex; dizziness, lightheadedness, drowsiness; mild euphoria or mild anxiety; mild clouding of mental functions; slight pupillary constriction.

Gastrointestinal: nausea, vomiting, constipation.

Other: itching sensation on the skin.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[4]

Intensification of low-dose effects may occur; duration of effects increases with size of the dose. In addition:

1. Sensitivity and emotional response to painful stimuli decrease.

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[1] Intravenous injection is rare, as it can produce severe flushing of the skin, puffy face, and occasionally severe drop in blood pressure.

[2] Single doses within the therapeutic range administered orally to nontolerant persons to a maximum of 200–250 mg per day in divided doses.

[3] When both are administered by subcutaneous injection, codeine 120 mg = morphine 10 mg; however, a principal advantage of codeine is that is retains approximately two-thirds of its potency when administered orally.

[4] Single doses in excess of the therapeutic range administered orally to nontolerant persons, or lower doses in particularly sensitive individuals.

2. In some users there is increasing agitation, and in others euphoria or sedation may occur.
3. Ability to concentrate is increasingly impaired.
4. There is a gradual decline in blood pressure and in some cases rapid and irregular heartbeat.
5. There is progressively slower and more shallow breathing.

At very high doses (i.e., overdose), codeine can produce tremors, seizures, delirium, coma, filling of the lungs with fluids, shallow and markedly reduced rate of breathing, low blood pressure, abnormally rapid heart rate, and pinpoint pupils.

EFFECTS OF LONG-TERM USE

Adverse consequences directly related to long-term codeine use include: mood instability,[5] pupillary constriction (which impairs night vision), constipation, reduced libido, menstrual irregularity, and certain types of respiratory impairment. Restlessness, tension, and muscle twitches have been observed in chronic high-dose abusers.

LETHALITY

Deaths from overdose exclusively of codeine have infrequently occurred in adults; however, severe overdose can result in seizures, delirium, coma, cardiac arrest, and death from respiratory arrest. The lethal dose in nontolerant adults is estimated to be 0.5–1.0 grams (500–1,000 mg).

Large doses of codeine preparations containing ASA can result in acute salicylate poisoning.

TOLERANCE AND DEPENDENCE

Tolerance

When codeine is taken regularly and very frequently for an extended period of time, even in low to moderate doses, tolerance can gradually develop to its analgesic, cough-reflex suppressant (antitussive), and mild euphoric effects. Higher daily doses may then become necessary to produce the desired effects.

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[5] This is due to the relatively short duration of action of codeine, i.e., four to six hours.

Physical Dependence/Withdrawal

Instances of physical dependence on codeine are not common; however, a definite withdrawal syndrome occurs upon abrupt termination of chronic high-dose abuse. Symptoms are similar to but milder than those observed during morphine withdrawal. Symptoms tend to appear about eight hours after the last dose, peaking in intensity by the second day and usually disappearing within less than a week. Early symptoms generally include anxiety, yawning, sweating, watering eyes, nasal discharge, and a period of restless sleep. Later symptoms are gooseflesh, pupillary dilation, tremors, muscle twitches, alternations between chills and flushing, aching in the bones and muscles, and loss of appetite.

Psychological Dependence

Psychological dependence on codeine may occur when it is taken very frequently for extended periods of time, even with low daily doses. Psychologically dependent users continue to use the drug on a regular basis even after tolerance has developed to their typical daily dose and the psychoactive effects are substantially diminished. The user has a persistent craving for the psychological effects, and ensuring that there is a sufficient supply of the drug may take on central importance; the user is likely to experience psychic distress if codeine is temporarily unavailable.

PATTERNS OF USE

In Canada, codeine is the only narcotic analgesic which can be obtained without prescription (in small amounts per unit dose in combination drugs). Because it is widely available both as a cough-reflex suppressant and as a pain reliever, like other widely available psychoactive drugs it is probably subject to some abuse.

Codeine is also reported to be used, often in hazardously large quantities, by those physically dependent on heroin or other potent narcotic analgesics; however, these users ordinarily resort to codeine when they are attempting to postpone withdrawal sickness and their preferred drug is not available. Although codeine is effective in at least partially suppressing heroin withdrawal sickness, the amount required may also produce grand mal seizures and possibly death due to respiratory arrest.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of codeine is low. Its euphoric and analgesic effects are relatively mild. Although codeine phosphate can be injected, intravenous administration (the route preferred by those who inject narcotic analgesics) can be hazardous.

Inherent Harmfulness

In low to moderate doses, adverse effects of codeine are usually both few and mild; however, the potential danger of CNS-stimulant effects at very high doses tends to limit use to amounts which generally do not produce the intensity of desired effects sought by experienced abusers of narcotic analgesics.

Availability

The abuse potential of codeine is enhanced by the relative ease of obtaining the higher-potency prescription codeine products (and, probably to a lesser extent, the availability of over-the-counter codeine products). Many of those dependent on more powerful narcotic analgesics acknowledge that their earliest experiences with drugs in this class were with codeine.

Diethylpropion

DRUG CLASS: CNS STIMULANT;
APPETITE SUPPRESSANT

SYNOPSIS

Diethylpropion is a central nervous system (CNS) stimulant which produces effects similar to but less intense than those of the amphetamines. It is legally obtainable only by prescription, and its medical indication is restricted to use in a short-term program of weight reduction. Although it was initially believed to be a "safe" diet pill, it is now understood to possess many of the same unfavorable attributes found in the amphetamines. With chronic high-dose use, a toxic state may result which is clinically identical to amphetamine psychosis. Tolerance to its effects develops fairly rapidly, and prolonged use can lead to both physical and psychological dependence. Because of recent reports of mounting abuse in Canada, diethylpropion has now been classified as a controlled drug.

DRUG SOURCE

Produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

DIP, Nobesine, Regibon, Tenuate.

STREET NAMES

None in common use; however, most stimulant drugs are referred to on the street as "uppers."

COMBINATION PRODUCTS

None in use.

MEDICAL USES

Only for short-term use (i.e., a few weeks) in a weight reduction program under medical supervision.

PHYSICAL APPEARANCE

Diethylpropion occurs as a white crystalline powder soluble in water and in alcohol.

DOSAGE

Medical

25 mg three times daily, or one 75 mg controlled-release tablet daily in mid-morning.

Nonmedical

There are case-history reports of use in excess of one gram (1,000 mg) per day. For chronic abusers, daily dosage increases as tolerance develops.

ROUTES OF ADMINISTRATION

Oral, by capsule; but injection routes have also been reported among abusers.

EFFECTS OF SHORT-TERM USE: LOW DOSES[1]

CNS, behavioral, subjective: euphoria, heightened feelings of well-being; overstimulation, nervousness, restlessness; dizziness; insomnia; headache; in rare instances, psychotic episodes. Increased alertness and postponement of fatigue often occur.

Cardiovascular: palpitation, increased heart rate; elevation of blood pressure; chest pain; irregular heartbeat.

Gastrointestinal: dry mouth; nausea, vomiting, abdominal pain, diarrhea, constipation.

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[1] Single doses within the therapeutic range up to 75 mg per day in nontolerant users.

Other: allergic reactions; impotence, changes in libido, menstrual imbalance.

It has been reported that the above effects tend to be of low frequency and are rarely severe enough to prompt discontinuation of therapy.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[2]

Intensification of the low-dose effects may occur as well as any of the following:

CNS, behavioral, subjective: excitation, agitation; pupillary dilation; slurred speech, motor incoordination, tremor; very rapid reflexes. On rare occasions toxic psychosis characterized by hallucinations and paranoid delusions has been reported.

Cardiovascular: chills and/or fever.

Hazardous dose levels may cause severe agitation, convulsions, coma, and circulatory failure.

EFFECTS OF LONG-TERM USE

Chronic heavy use of diethylpropion can result in a toxic state identical to amphetamine psychosis (a disorder resembling acute paranoid schizophrenia), and abstinence can lead to the reversal of the syndrome.

What little evidence is available indicates that tolerance to the subjectively pleasurable effects of diethylpropion develops within 24–72 hours after heavy repeated administrations. After this, uninterrupted use usually results in physical discomfort, agitation, and paranoid thinking. A pattern of chronic abuse of diethylpropion may therefore be similar, in some respects, to that observed in chronic amphetamine abuse. Experienced amphetamine abusers, however, regard diethylpropion as a poor substitute for their drug of preference. Its mood-elevating properties are considerably less pronounced than those produced by an equivalent dose of amphetamines, and compensatory dose

[2] Doses above the medically recommended level in nontolerant users, and lower doses in particularly sensitive individuals.

increases often result in the above-mentioned adverse effects. Both factors may militate against its extended abuse at high doses.

LETHALITY

Severe overdose can lead to convulsions, coma, and circulatory collapse. Although death may result, deaths from diethylpropion overdose are extremely rare.

TOLERANCE AND DEPENDENCE

Tolerance to the appetite-suppressant (anorectic) effect can develop within a few weeks. However, an increased dosage tends to be unattractive, since it may cause such symptoms as irritability and nervousness. Tolerance to the subjectively pleasurable effects can develop rapidly, and attempts at increasing the dose to highly excessive levels to compensate for tolerance may increase the possibility of a toxic psychotic reaction.

Physical dependence can occur with protracted high-dose abuse. Withdrawal symptoms following abrupt cessation of use may include extreme fatigue, ravenous appetite, depression, and marked agitation; however, these symptoms are not as severe as is the case with amphetamine withdrawal.

Psychological dependence on diethylpropion has been reported. It is characterized by a preoccupation with and a compulsive need to continue taking the drug even when it no longer produces significant psychoactive effects. The craving for these effects may be so intense that, if diethylpropion is temporarily unavailable, distress or even feelings of panic may be experienced.

PATTERNS OF USE

Reports of mounting abuse in Canada have recently (in 1978) led to diethylpropion's being classified as a controlled drug. Its increased popularity appears to be related to a decline in the availability and quality of street amphetamines.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of diethylpropion is high, but not as high as that of cocaine, amphetamine, and methamphetamine. When diethylpropion is injected, the euphoria and central stimulation it produces are less powerful than with these other drugs. Therefore, diethylpropion is usually not the drug of choice for most stimulant abusers.

Inherent Harmfulness

Inherent harmfulness of diethylpropion is not a major factor restricting its abuse. Its potentially hazardous effects are not ordinarily manifested at the low to moderate doses at which the drug is typically abused. Some experienced users take this drug at very high dose levels; they are generally aware of the heightened risks and also willing to accept them.

Availability

Reclassification of diethylpropion to its current status as a controlled drug has greatly reduced its previous widespread abuse.

Disulfiram

DRUG CLASS: METABOLIC INHIBITOR; "PROTECTIVE" DRUG

SYNOPSIS

Most commonly known by its trade name, Antabuse, disulfiram is a drug taken daily by mouth to deter the consumption of alcohol.[1] For this reason it is known as a "protective drug."[2] Disulfiram interferes with the normal metabolism of alcohol so that acetaldehyde, an intermediary metabolite of alcohol, rapidly accumulates in the bloodstream instead of being further metabolized. The resultant acetaldehyde poisoning (i.e., the alcohol/disulfiram reaction) causes severe but temporary physical discomfort. Some of the typical symptoms include weakness, vertigo, marked decrease in blood pressure, throbbing in the head and neck, extreme flushing of the face, headache, chest pain, labored breathing, nausea, and vomiting.

For those alcoholic patients who reliably self-administer disulfiram, the knowledge that even small amounts of alcohol can prompt such a highly noxious reaction is sufficient to deter any alcohol consumption. Disulfiram therapy is generally viewed to be most beneficial to those patients who are simultaneously undergoing a comprehensive treatment and rehabilitation program.

In the absence of alcohol in the body disulfiram usually produces few and relatively mild side effects. In the presence of alcohol only a small minority of patients suffer serious medical consequences resulting from the alcohol/disulfiram reaction. Because most of these consequences involve the cardiovascular system, patients with a history of cardiovascular disorders are normally excluded from disulfiram therapy.

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[1] Surgical implantation of disulfiram has been the subject of extensive clinical research, but the results have been generally disappointing.

[2] Another "protective" drug which produces effects similar to those of disulfiram is calcium carbimide, marketed under the trade name Temposil. (See section 5.)

DRUG SOURCE

Disulfiram is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Antabuse.

STREET NAMES

None.

COMBINATION PRODUCTS

None.

PHYSICAL APPEARANCE

Disulfiram appears as a white or off-white odorless powder very slightly soluble in water and soluble in alcohol.

DOSAGE

Medical

The initial oral dose is typically 500 mg, and is ordinarily administered to the patient after several days of complete abstinence from alcohol. Daily maintenance dose is between 125 and 500 mg. Experimental implantation of disulfiram usually involves a total quantity of approximately 1 gram (1,000 mg) in the form of a disc surgically inserted into the fatty tissue of the abdomen once every several months.

Nonmedical

Not applicable.

ROUTES OF ADMINISTRATION

Orally in daily single or divided doses or by implantation once every several months.

EFFECTS OF SHORT-TERM USE: LOW DOSES[3]

In the absence of alcohol, a single dose of disulfiram usually does not produce noticeable side effects, except for an initial period in which drowsiness and lassitude can occur.

Once present in the body, the effects of disulfiram on a person who ingests or inhales even small amounts of alcohol can be pronounced. Mild to severe distress can result from ingesting a single dose of cough syrup containing alcohol, from inhaling rubbing alcohol, perfume, nail polish, or hair tonics, or from ingesting as little as 7 ml of ethyl alcohol (i.e., less than one-half of a standard drink).

Although the alcohol/disulfiram reaction is characteristically very unpleasant,[4] serious or life-threatening complications are unusual in otherwise healthy adults when they are carefully supervised by a physician. The typical syndrome occurs within a few minutes after alcohol ingestion, and can include:

CNS, behavioral, subjective: weakness, vertigo, blurred vision.

Cardiovascular: extreme flushing of the face, throbbing in the head and neck, palpitations, fainting, headache (possibly severe), rapid and marked decrease in blood pressure, increased pulse rate, chest pain.

Respiratory: gasping or labored breathing.

Gastrointestinal: dry mouth and throat, nausea, and vomiting.

These effects may be experienced for a few hours; the exhausted patient then typically falls asleep and upon awakening is usually completely recovered.

Hazardous reactions are unusual; however, they can include marked respiratory depression, cardiovascular collapse, extreme drop in blood pressure, acute congestive heart failure, obstruction of the coronary artery, coma, and convulsions.[5]

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[3] Single doses of 125–500 mg, taken orally.

[4] Effects are likely to be more intense after regular use of disulfiram has been instituted (i.e., usually a few days after the initial administration), and they may last for a few hours. Knowledge of these effects serves as a deterrent to alcohol use; hence the drug serves as a "protective" agent. Patients must be cautioned against any use of alcohol for up to two weeks after the termination of disulfiram therapy, since disulfiram is very slowly excreted from the body.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[6]

Drowsiness and fatigue are more pronounced than at low doses, and the alcohol/disulfiram reaction may be more intense.

Nonlethal overdose can produce elevated body temperature, lethargy, depression, inflammation of peripheral nerves, cerebellar dysfunction, impairment of intellectual functioning, and parkinsonism-like symptoms.

EFFECTS OF LONG-TERM USE

With regular use, most side effects are mild and tend to disappear within a few weeks, although in some patients they can be quite severe. These side effects can include:

CNS, behavioral, subjective: fatigue, lassitude, morning drowsiness and difficulty in arising, sedation; tremor, restlessness, dizziness. Depression and anxiety are reported by some patients; however, these may have been symptoms suppressed by alcohol use and merely unmasked by abstinence. Overt psychosis has also occasionally occurred, sometimes prompted by excessively high doses of disulfiram or interactions with certain other drugs. It may also represent the unmasking of latent psychosis.

Cardiovascular: headache.

Gastrointestinal: a variety of mild gastrointestinal disturbances, garlic breath, sometimes a metallic taste.

Other: skin eruptions, allergic dermatitis (which responds well to topical antihistamines), burning or itching sensations on the skin; reduced libido.

[5] The need for careful medical screening, particularly to eliminate those patients with a history of cardiovascular disease or convulsions, is essential, as is the continued supervision of those patients accepted for disulfiram therapy.

[6] Single doses in excess of the therapeutic range, or lower doses in sensitive individuals.

The rate of degradation of certain other drugs such as phenytoin (e.g., Dilantin) and some anticoagulants may be considerably slowed in patients undergoing disulfiram treatment, thus prolonging duration of action of the other drug and requiring adjustments of the patient's dosage schedule.

DISULFIRAM IMPLANTATION

For disulfiram to be an effective pharmacological deterrent to alcohol consumption, the patient must fully cooperate and be willing to take the drug regularly. However, many alcoholic patients have proven unreliable with regard to taking disulfiram, seeking rather to continue to drink with impunity.

Because subcutaneously implanted disulfiram is slowly eliminated from the body,[7] it was thought that this procedure might produce more beneficial results in unreliable patients. However, after over two decades of clinical research with large numbers of patients, the results of disulfiram implantation have generally been disappointing. One recent summary concluded: "Pharmacologically speaking, the implantation . . . does not seem to have more than a placebo action . . . and side effects [i.e., of the alcohol/disulfiram interaction] are likely to be irritant rather than toxic" (Fastner, 1977, p. 382).

LETHALITY

Cardiovascular collapse and death have occasionally been caused by the alcohol/disulfiram reaction. A few cases of severe brain damage in very young children have resulted when they have accidentally taken disulfiram in large quantity.

TOLERANCE AND DEPENDENCE

There is no evidence that tolerance develops to the "protective" effects of disulfiram. However, tolerance to most of the non-alcohol-related side effects develops fairly rapidly, within a few weeks.

Dependence on disulfiram does not occur.

PATTERNS OF USE

Most experts now agree that the primary value of disulfiram is as an adjunct to a more comprehensive treatment program, particularly for patients who reliably take the drug. Disulfiram treatment provides a means for preventing alcoholics from drinking while their other problems are being actively sorted out—for example, through Alcoholics Anonymous or professional counseling—and it is effective only if they have a genuine desire to change the disruptive aspects of their lifestyle. In fact, there is no substantive evidence that disulfiram therapy, when undertaken without any additional treatment, is more effective than a placebo in determining future drinking once therapy has been terminated.

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[7] It may remain up to several months before it is completely eliminated.

ABUSE POTENTIAL

Disulfiram has no potential for abuse.

REFERENCE

Fastner, Z., Miscellaneous drugs, in *Side Effects of Drugs Annual I: Amsterdam Excerpta Medica*, M.N.G. Dukes (Ed.), 1977.

Ethyl (Beverage) Alcohol

DRUG CLASS: SEDATIVE/HYPNOTIC

SYNOPSIS

Ethyl alcohol (beverage alcohol, ethanol)[1] is used extensively throughout the world, predominantly for recreational and sacramental purposes; for this reason, it is often not thought of as a drug. However, ethyl alcohol produces a range of central nervous system (CNS) effects quite similar to those of other sedative/hypnotic drugs. At low to moderate doses, it usually produces a general feeling of well-being and mild relaxation of inhibitions. As the dose is increased per unit time, the drinker experiences progressively greater levels of intoxication characterized by increasing degrees of cognitive, perceptual, and motor impairment. Greater relaxation of emotional controls under these circumstances often results in actions and attitudes that are socially unacceptable, frequently taking the form of aggressive or hostile behavior. On the other hand, some intoxicated persons become so depressed that they make serious suicide attempts.

When consumed at very high doses, ethyl alcohol can produce severe respiratory depression; deaths from respiratory arrest have resulted from blood alcohol concentrations of approximately 0.5%. Much lower doses can be lethal when taken in combination with other CNS-depressant drugs.

Chronic abuse of ethyl alcohol also poses serious health risks to the drinker. Long-term use most adversely affects the liver and other parts of the gastrointestinal system, as well as the central nervous system, especially the brain. An extreme manifestation of damage to the former would be cirrhosis of the liver, and to the latter, increasingly severe memory impairment.

Regular use creates tolerance to higher doses, and ultimately the drinker is less able to achieve the desired pleasurable effects at any dose level. Nonetheless, because highly tolerant drinkers are also often physically dependent on alcohol, they continue to consume high doses in order to avoid the onset of withdrawal symptoms. Abstinence after protracted drinking bouts can result in a withdrawal syndrome sufficiently severe to cause death.

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[1] Ethyl alcohol is to be distinguished from two related compounds both of which are toxic: isopropyl alcohol and methyl alcohol (see articles below).

DRUG SOURCE

Ethyl alcohol can be produced in two ways: (1) by fermentation and distillation from agricultural products; and (2) by chemical manufacture for industrial purposes.

Beverage alcohol by law and custom must be ethyl alcohol made from agricultural products by the process of fermentation and, where applicable, distillation. Where supplementation is required, as in liqueurs and fortified wines, the added alcohol must also be produced by fermentation and distillation of agricultural products. Wine and beer are fermented to produce beverages with up to 14% alcohol content; distilled spirits and liqueurs (whiskey, brandy, vodka, etc.) are fermented, then distilled to raise the alcohol content. The distillate is then adjusted (usually by adding water) to the desired concentration, which is usually between 15% and 40%. Some products are not diluted, and may contain up to 95% alcohol.

TRADE NAMES

Ethyl alcohol is itself not marketed for any specific medical use; however, it is an ingredient in certain products marketed for medicinal purposes (see Combination Products below).

STREET NAMES

Booze.

COMBINATION PRODUCTS

Alcoholic beverages are often combined with nonalcoholic mixes and/or other alcoholic beverages. Some alcohol abusers combine their beverage with other drugs of abuse, particularly other sedative/hypnotics, such as barbiturates—a dangerous practice.

Because ethyl alcohol is an excellent solvent, relatively small amounts are combined with other ingredients in many cough syrups and in certain other medicinal products which are prepared in solution for oral administration. Alcohol is also a constituent of many mouthwashes and shaving lotions. These nonbeverage products have been used by youths and impoverished alcoholics to produce a mild state of intoxication.

MEDICAL USES

In the past, ethyl alcohol was used to induce sedation, sleep, and anesthesia. However, it is no longer used for the last purpose, because effects at the high doses generally required to induce anesthesia are uncontrollable and can include dangerous depression of the respiratory control centres in the brain.

Some physicians recommend the occasional use of alcohol as a mild sedative and to induce sleep, particularly for elderly patients. They reason that to prescribe sedatives and sleeping pills might suggest to the patient a state of illness, whereas a small dose of sherry, for example, tends to suggest a more benign state of affairs. Alcohol can also improve both appetite and digestion.

PHYSICAL APPEARANCE

Ethyl alcohol is a clear liquid. The appearance of beverage alcohol depends on the particular diluents and additives with which it is combined.

DOSAGE

Medical

As noted above, small doses of alcohol are sometimes recommended by physicians.

Nonmedical

A standard drink served, for example, in North American hotels and restaurants contains approximately 0.6 oz (1.7 cl or 17 ml) of *absolute* ethyl alcohol. This can be in the form of approximately 1.5 oz (4.4 cl) of distilled spirits (40% absolute ethyl alcohol), 5 oz (14.8 cl) of table wine (12% absolute ethyl alcohol), 3 oz (8.9 cl) of fortified wine such as sherry (20% absolute ethyl alcohol), or 12 oz (35.5 cl) of regular

Canadian beer (5% absolute ethyl alcohol). The degree of intoxication does not depend on the type of alcoholic beverage but rather on the amount of *absolute* ethyl alcohol consumed on a given drinking occasion.

There is extreme variation in the amount different individuals consume during a single drinking episode. A light drinker may have as little as a single serving of wine with dinner: i.e., 5 oz of table wine, or 1.7 cl (or less) of absolute ethyl alcohol. A highly tolerant alcoholic, on the other hand, may drink as much as several bottles of spirits during a continuous binge: i.e., more than 100 oz of spirits, or 120 cl (and up) of absolute ethyl alcohol.

ROUTES OF ADMINISTRATION

Ethyl alcohol is ingested by mouth.

EFFECTS OF SHORT-TERM USE: LOW TO MODERATE DOSES[2]

Alcohol is rapidly absorbed into the bloodstream from the small intestine and less rapidly from the stomach and colon. Its absorption rate, however, is affected by such factors as the type and dilution of the beverage as well as the presence in the stomach of food. Milk is reported to be particularly effective in retarding absorption. Once the alcohol has passed into the blood, however, no food or beverage can retard, shorten, or interfere with its effects. In the average adult, the rate of metabolism is about 1.0 cl (10 ml) or 0.3 oz of absolute ethyl alcohol per hour, although this rate can vary markedly between individuals, depending on liver size, acquired tolerance, and genetic factors.

CNS, behavioral, subjective: CNS effects tend to be dose related—that is, proportional to the amount of ethyl alcohol in the bloodstream. As the level in the bloodstream increases, the range and intensity of effects also increase; however, there are significant individual differences in the response.

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[2] Single doses of up to 1.7 oz (5.1 cl) of absolute ethyl alcohol (three standard drinks) consumed by nontolerant persons.

Although alcohol is a CNS depressant, its usual early effects are heightened activity and disinhibition. While this "stimulation" effect seems to be paradoxical, it actually results from depression of the inhibitory and behavioral control centres of the brain and is not true stimulation. Some people in fact may feel drowsy shortly after consuming even small quantities.

Many drinkers tend to feel gregarious, expansive, jovial, relaxed, and more self-confident. Others may become hostile, depressed, and withdrawn. Still others may experience mood swings. These emotional responses can be greatly affected by the drinking context as well as by the amount of alcohol consumed.

As the dose increases within this range, cognitive processes and memory may become moderately impaired. These effects are usually manifested in decreased insight, sometimes impaired judgment, concentration difficulties, interference with thought and communication processes, and impairment of recent memory. For some drinkers, even low to moderate amounts of alcohol can produce such profound effects as confusion and disorganized thinking.

Several perceptual and motor functions may also be adversely affected by low to moderate doses: ability to estimate distance (critical to the operation of an automobile, motor boat, or snowmobile) may be impaired, as well as the perception of time; there may be a dulling of the perception of pain, a reduced reflex response, an increased reaction time, impairment of fine motor dexterity, and in some cases impairment of gross motor functions and slurred speech.

Cardiovascular: Dilation of the cutaneous blood vessels is common and tends to produce warm and flushed skin. However, body temperature may actually be slightly reduced as a result of increased perspiration.

Respiratory: Moderate doses mildly stimulate respiration in some drinkers, while in others respiration may be slightly depressed.

Gastrointestinal: increased gastric secretion.

Other: increased urine output; increased or reduced libido.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

A state of intoxication associated with higher doses of alcohol is characterized by increasing to the extreme the relaxation of the control functions of the higher brain centres; following a period of activity, sleep is likely to occur.

Drinkers frequently exhibit behavior which is unlikely to occur when they are sober. Emotions tend to be highly exaggerated and can range from effusive conviviality to outright aggression. Mood swings can occur abruptly and are often accompanied by a reduced level of frustration tolerance. Under such conditions, typical external controls, such as setting and companions, are frequently ineffective in restraining socially unacceptable behavior; in fact, attempts at restraint may even exacerbate the undesirable behavior.

Cognitive, judgmental, and memory functions may be highly impaired, and thinking and communication can be so disorganized as to prevent the drinker from being understood by others; slurring further impairs the high-dose drinker's attempts to communicate. Memory impairment may be so pronounced that the drinker may be unable to recall, the following day, much or any of the previous night's events; that is, a partial or total blackout is experienced.

Perceptual and motor dysfunctions are highly evident. With increasing CNS depression, the experience of both external and internal stimuli progressively declines to a point where even painful stimuli do not evoke a response. (In effect, the higher perceptual centres are not receiving the message.) Concurrently, control of voluntary motor functions progressively deteriorates to the point where the drinker is unable to rise or even continue to stand without assistance—much less walk. (In effect, higher centres controlling motor activity and balance are not sending the message.)

High doses of ethyl alcohol induce sleep; very high doses produce stupor or coma. These effects all result from progressively greater CNS depression. The sleep produced by high doses of alcohol differs from normal sleep in the following respects:

1. It can be very difficult to arouse a person in alcohol-induced sleep to full consciousness.

[3] Single doses of 1.7 oz (5.1 cl) or higher of absolute ethyl alcohol consumed by nontolerant persons, or lower doses in particularly sensitive individuals.

2. REM sleep (those recurring phases of sleep characterized by continuous dreams and rapid eye movement) is substantially suppressed.
3. Upon awakening, the person is quite likely to complain of having slept poorly and feeling groggy.

Hangover is a probable aftereffect of high-dose alcohol consumption. It is a manifestation of mild withdrawal phenomena and is typically characterized by fatigue, headache, nausea and possibly vomiting, shakiness, bloodshot eyes, and a general feeling of malaise. (While there are literally dozens of "home remedies" for hangover, the fact remains that there is currently no known effective cure.)

Other physiological effects of higher doses are similar to, but more intense than, the aforementioned effects of low to moderate doses. The principal toxic effect of acute high doses is respiratory depression; however, dangerous levels of respiratory depression are unlikely to occur in healthy adults unless very high doses (i.e., overdoses) are consumed. At severe overdose levels, significant cardiovascular depression can occur. These hazardous effects may occur at lower doses if the drinker also consumes other CNS-depressant drugs.

EFFECTS OF LONG-TERM USE

The adverse physical and psychological effects of chronic abuse of alcohol are numerous, and some are potentially life-threatening. Some of these harmful consequences are primary—that is, they may directly result from prolonged exposure to the toxic effects of alcohol (an example would be liver disease). Others are secondary—that is, they are indirectly related to chronic alcohol abuse and would result from such causes as long-term nutritional deficiencies.

Individual susceptibility to alcohol-related diseases and conditions varies greatly; however, moderate and occasional use in otherwise healthy adults is unlikely to present significant health problems. For people with certain types of health problems, such as peptic ulcer or liver disease, even small amounts of alcohol may result in potentially harmful complications.

It is not possible to determine the specific amount and frequency of alcohol consumption which is likely to produce health impairment in any given individual. Nonetheless, on an average basis, a daily dose of

5.0–7.5 cl *absolute* ethyl alcohol (i.e., 4.2–6.3 oz of spirits) has been shown to increase significantly the risk of liver pathologies and also certain types of cancer. When alcohol is taken in larger daily doses, the risk of serious disease is further enhanced. The most significant adverse consequences of chronic high-dose abuse include the following:

Behavioral and CNS[4]

Certain psychiatric symptoms, such as emotional depression and anxiety, are much more commonly manifested among alcoholics than among the general population. A vicious circle often occurs when the alcoholic seeks relief from these chronic symptoms through alcohol; for example, as tolerance develops to an anxiety-relieving dose, the drinker is obliged to consume ever greater amounts. Furthermore, once the drinker has become even mildly physically dependent on alcohol, its absence from the body is in itself likely to produce intense anxiety, a common symptom of early withdrawal.

When compared to nonalcoholics, alcohol abusers have higher rates of divorce, absenteeism from work, and suicide. They also change jobs more frequently and are far more likely to be victims and/or perpetrators of violence. Furthermore, alcoholics rank among the highest of all psychiatric groups in terms of rate of admission to inpatient psychiatric services.

For many alcoholics, CNS impairment may not be obvious even after years of heavy drinking. Blackouts, however, can occur early in an alcoholic's drinking career, and are characterized by amnesia for events occurring during periods of intoxication; they tend to become progressively more complete with the passage of time and to occur more frequently. Memory for recent events other than those occurring during intoxication also tends to become increasingly impaired. Emotional restraint, particularly when drinking, gradually (or in some instances rapidly) deteriorates and the probability of socially unacceptable behavior increases. As with chronic abusers of other sedative/hypnotics, alcoholics are likely to suffer insomnia and, when sleep does occur, to feel poorly rested upon awakening.

After many years of regular heavy drinking, the chronic alcoholic may begin to experience primary symptoms of organic impairment, which gradually become more serious and more overt: confusion, articulation difficulties such as persistent slurring even when sober, impairment of perceptual/motor functions, and the increasing loss of ability to reason abstractly. Damage to the cerebellum, a brain structure which controls certain types of gross motor functions, can produce a type of gait which is quite similar to that observed in the highly intoxicated; this gait persists in the deteriorated alcoholic even after extended periods of sobriety.

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[4] Much research and speculation has been devoted to attempting to define an "alcoholic personality." Unfortunately, the collective results of this research fail to reveal a valid clinical profile for such a personality.

Decades of nutritional deficiency caused by inadequate diet, chronic gastritis, and impaired liver metabolism due to alcohol consumption can result in brain damage so severe that alcoholics are totally unable to care for themselves. One severe condition, the Wernicke-Korsakoff syndrome, is in part characterized by an all-encompassing and profound confusion, disorientation, general fatigue, apathy, amnesiac confabulation (i.e., loss of memory so great that the patient resorts to reporting an utterly false and at many times bizarre life history), or, in some cases, permanent amnesia without confabulation. This condition typically requires permanent institutionalization.

Several other neurological disorders of uncertain cause, such as peripheral neuropathy and the degeneration of the corpus callosum (fibers which connect the two cerebral hemispheres), may be caused by protracted exposure to alcohol.

Gastrointestinal

Acute gastritis during drinking episodes is the most likely explanation of the high incidence of nausea, vomiting, and loss of appetite in chronic alcoholics. Other gastrointestinal disorders which have a significantly higher incidence among alcoholics than among the general population include peptic ulcer, cancer of the esophagus, and chronic pancreatitis. However, the most common disease states associated with alcoholism are liver disorders: fatty liver, alcoholic hepatitis, and cirrhosis (i.e., the proliferation of fibrous tissue which changes the normal lobular shape of the organ). Cirrhosis is a leading cause of death among alcoholics. Death may result either from grossly impaired liver function or from gastrointestinal hemorrhage caused by abnormally high blood pressure in the veins of this area.

Sexual Function

Impotence in male alcoholics and menstrual irregularity in female alcoholics are very common.

Cardiovascular

Alcoholic cardiomyopathy (deterioration of the muscles of the heart) is thought to result from the toxic effects of ethyl alcohol on the heart; it may be so severe as to cause death from heart failure. Certain types of recurrent cardiac arrhythmias are also believed to be associated with chronic alcoholism. Other types of cardiac disorders occur more frequently in alcoholics than in the general population; however, because alcoholics tend also to be heavy smokers, the direct contribution of alcohol to these conditions is not yet clear.

Respiratory

It is not unusual for alcoholics to suffer chronic respiratory disorders; however, heavy smoking is undoubtedly the primary contributing factor.

LETHALITY

Severe overdose may result in stupor or coma, with cold and clammy skin, low body temperature, respiratory depression, and accelerated heart rate. The probability of lethal consequences is increased if the comatose state persists beyond 12 hours. Deaths from respiratory arrest have resulted from blood concentrations in the range of 0.5% absolute ethyl alcohol.

Alcohol figures prominently in many successful suicides and accidental deaths every year. These fatalities most typically result from overdose combinations of alcohol and other CNS-depressant drugs—sedative/hypnotics, narcotic analgesics, and occasionally minor tranquillizers.

Death may also occur during severe alcoholic withdrawal.

TOLERANCE AND DEPENDENCE

Tolerance

Chronic alcohol use results in an increased capacity to metabolize this drug. When the liver metabolizes a given dose so quickly that a significant blood alcohol level is not maintained, metabolic (dispositional) tolerance is said to have developed. Without a significant blood alcohol level, the psychoactive effects of alcohol cannot be experienced. The drinker must then either increase the dose or frequency of administration in order to regain the desired effects or abstain for a period of several weeks to regain the original sensitivity to the drug.

Along with metabolic tolerance, the chronic abuser develops a concurrent CNS (functional) tolerance in which the brain and other parts of the CNS become less sensitive to the effects. This form of tolerance can also be overcome either through a period of abstinence or through increasing the regular dose.

Cross-tolerance also develops between alcohol and many other sedative/hypnotic drugs: that is, once tolerance to the desired effects of alcohol is present, the user will also be tolerant to the same desired effects produced by most other sedative/hypnotics at psychoactively equivalent doses.

Psychological Dependence

Psychological dependence on alcohol may occur with regular use irrespective of the size of the daily dose. It may also occur in irregular users who are likely to consume alcohol only under certain conditions, such as prior to and during social occasions. This form of dependence refers to a craving for the psychological effects, although not necessarily in doses which would result in intoxication. For psychologically dependent drinkers, the temporary unavailability of alcohol tends to produce anxiety and, for some, feelings of panic. Furthermore, psychologically dependent drinkers are likely to resist terminating the use of alcohol even when substitutes are available that are relatively effective for reducing anxiety and are at the same time less harmful (e.g., minor tranquillizers).

Physical Dependence/Withdrawal

Physical dependence on alcohol can result from chronic abuse and tends to be a function of the amount of absolute ethyl alcohol consumed, the length of exposure (drinking chronicity), and the frequency of drinking episodes. It is not a function of the form in which it is consumed (i.e., beer, wine, or spirits). Abrupt termination following protracted heavy use can result in severe withdrawal sickness. Generally, there are three consecutive phases in the withdrawal syndrome, although there can be considerable overlap among the phases, and the second phase does not universally occur.[5]

[5] In mildly dependent persons only the first phase tends to occur and is ordinarily not severe.

The initial phase can begin as rapidly as a few hours after cessation of drinking. Declining blood alcohol levels may still be as high as 100 mg/100 ml (0.1%) or higher when early characteristic symptoms are observed. These include increasingly severe tremulousness (the "shakes"), profuse perspiration, weakness, and alcohol-seeking behavior (or another drug may be sought). Other symptoms which tend to be manifested are agitation, headache, anorexia, nausea and vomiting, abdominal cramps, abnormally rapid heartbeat, and hyperreflexia (exaggerated and rapid reflexes). If appropriate drugs or alcohol are not administered, visual and auditory hallucinations—alcoholic hallucinosis—often ensue and increase in intensity. While acute alcoholic hallucinosis is most likely to occur during the first phase of withdrawal, observers have reported its occasional occurrence in some alcoholics who are still severely intoxicated.

The second phase, when it occurs, begins within 24 hours after the termination of drinking. This phase is characterized by grand mal seizures, which may range from one seizure to continuous severe seizure activity with little or no interruption (status epilepticus). Deaths due to traumatic injury have occurred during this phase.

The third and most protracted phase is commonly called delirium tremens ("DTs"). During this phase, the person is severely agitated, often appearing extremely confused and disoriented, and is almost continuously active. Very high body temperature and abnormally rapid heartbeat also occur. The hallucinations that characteristically occur during this phase are typically terrifying; they may be visual, auditory, or tactile—the last type being most commonly manifested as "bugs" or "little animals" crawling over the skin. These hallucinations are often accompanied by bizarre delusions, and the combination of symptoms may provoke violent behavior. For this reason and because of the possibility of accidental injury, restraints are generally necessary.

The third phase of withdrawal usually lasts for three to four days. Deaths during this period are not unusual and are most commonly caused by very high fever, cardiovascular collapse, or traumatic injury. Provided the person survives, withdrawal sickness subsides within five to seven days, by which time the person is severely exhausted and dehydrated.

The degree of cross-dependence between alcohol and barbiturates is considerable: each, in sufficient doses, can substantially (but not completely) suppress withdrawal symptoms induced by abstinence from the other. Furthermore, cross-dependence occurs to varying degrees (none complete) between alcohol and other sedative/hypnotic drugs, as well as between alcohol and the minor tranquillizers. For this reason, the barbiturate phenobarbital and the minor tranquillizers diazepam (e.g., Valium) and chlordiazepoxide (e.g., Librium) are often used to reduce the severity of alcoholic withdrawal.

PATTERNS OF USE

Virtually all available data indicate that over the past several decades there has been a worldwide trend toward substantially increased per capita alcohol consumption. The per capita increase in industrialized countries between 1960 and 1973 was greater than 40%. In many areas, it was considerably higher than that.

A 1981 survey of Ontario students in grades 7–13 found that alcohol was by far the most commonly used psychoactive drug. Over 75% acknowledged having consumed an alcoholic beverage at least once during the past 12 months. Perhaps more disturbing was the fact that slightly more than one in five of those who drank did so at least once a week. Given that the legal drinking age is 19 in Ontario, it would appear that there is a very high degree of social acceptance for alcohol use, whether legal or not.

Most researchers agree that the number of alcoholics in North America is approximately 3% to 4% of the adult population. There are two primary patterns of extreme alcohol abuse (alcoholism) in our society. The largest group are regular heavy drinkers who tend to drink daily or on most days. Surveys have found that these alcoholics are very likely to be preoccupied with alcohol even when they are not drinking. After many years of chronic abuse, the vast majority of this group are unable to achieve the highly pleasurable state of intoxication associated with their early drinking experiences. They tend to vacillate between extended periods of heavy drinking and brief periods of cutting down or abstaining. During the periods of heavy drinking they tend to deny that they have a drinking problem. When they do abstain, it is usually because of the threat of sanctions by legal authorities, employers, or family and friends. However, surveys indicate that only a small minority of alcoholics receive professional counseling for their drinking problem.

A second alcoholic pattern is called episodic, spree, or binge drinking. In this case, the alcohol abuser may function adequately for several days, weeks, or even months without drinking. For reasons which are not yet fully understood, the person periodically consumes very large quantities (76.9 cl or 26 oz of spirits or more, or 24 bottles of beer or more, per day) over several days or weeks. The binge usually commences on a weekend. Binge drinking usually terminates because the drinker experiences extreme physical discomfort as a result of the alcohol, because funds are depleted, because exhaustion is reached, or because behavior of some sort leads to arrest. Abrupt cessation of protracted binges often results in severe withdrawal sickness; in fact, binge drinkers admit that one major reason for extending the binge is their fear of withdrawal.

While the above are classic patterns, in the complex and pluralistic society of North America there are many other alcoholic drinking patterns. For example, some first- and second-generation drinkers of Southern European ancestry consume excessive amounts of wine on a daily basis, amounts that greatly exceed traditional levels of consumption with meals. While drunken behavior is not tolerated and is therefore unusual among this group, they have a very high rate of alcohol-related diseases.

ABUSE POTENTIAL

Dependence Liability

Ethyl alcohol can rapidly produce a state of pleasurable intoxication; it is also highly effective in reducing tension states. For these reasons, it is viewed to have a moderate dependence liability. In fact, most estimates suggest that as many as one in 20 drinkers has a dependence problem.

Inherent Harmfulness

The damaging physical effects of alcohol (like those of tobacco) may not be overt until several years after the commencement of regular heavy drinking. For this reason, its inherent harmfulness is unlikely to deter young heavy drinkers from their excessive consumption, especially since it produces such immediate gratification. However, social and legal sanctions applied against unacceptable behavior arising from abusive drinking compel many drinkers to monitor their intake on given drinking occasions.

Availability

The easy availability of alcoholic beverages also contributes to alcohol's high abuse potential—among the highest of all drugs in the world.

Glutethimide

DRUG CLASS: SEDATIVE/HYPNOTIC

SYNOPSIS

Glutethimide was introduced in 1954 and was originally intended as a safe and nonaddicting alternative to the barbiturates. In fact, its dependence liability has proven to be just as great, and when taken regularly at therapeutic or high abusive doses, or even in a single high dose, it has clearly demonstrated its capacity to be as dangerous as the barbiturates or even more so.

Single therapeutic doses can produce sedation and sleep depending on the size of the dose taken; at therapeutic dose levels, side effects are usually mild. Higher doses produce barbiturate-like euphoria. Still higher doses can produce coma and sometimes grand mal seizures. At overdose levels, the respiratory depression caused by glutethimide is not nearly as great as that resulting from barbiturate overdose; however, serious respiratory complications are common, and a number of deaths have resulted from this as well as from cardiovascular collapse.

Tolerance develops rapidly to the sedative, sleep-inducing, and euphoric effects of this drug. Chronic high-dose abuse results in severe physical dependence, and abrupt abstinence can produce a painful and life-threatening withdrawal syndrome. For reasons which are not understood, some medical users who regularly take daily doses of glutethimide within the therapeutic range have suffered a sudden onset of withdrawal symptoms even though they have not stopped taking the drug; this same phenomenon has also happened to regular high-dose abusers.

DRUG SOURCE

Glutethimide is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Doriden.

STREET NAMES

None in common use.

COMBINATION PRODUCTS

“Loads” (glutethimide plus codeine).

MEDICAL USES

- daytime sedation;
- preanesthetic sedation;
- induction of sleep.

PHYSICAL APPEARANCE

Glutethimide occurs as a white crystalline powder very slightly soluble in water and soluble in alcohol.

DOSAGE

Medical

- for daytime sedation—125–250 mg three times per day after meals;
- for induction of sleep—500 mg at bedtime.

Nonmedical

Initially, the user may take daily doses within the therapeutic range. With increased tolerance to the desired effects, the daily dose may be increased. Abusive daily doses of 5 grams (5,000 mg) are not unusual, and some highly tolerant abusers may take as much as 12 grams per day.

ROUTES OF ADMINISTRATION

Orally, by either capsule or tablet.

EFFECTS OF SHORT-TERM USE: LOW DOSES[1]

CNS, behavioral, subjective: The principal desired effects are relaxation and calmness; drowsiness may be sufficient to produce sleep. Also dizziness, lethargy, confusion, exacerbation of preexisting pain, blurred vision, sometimes anxiety and restlessness.

Cardiovascular: headache.

Gastrointestinal: dryness of the mouth, nausea and vomiting, loss of appetite.

Other: Hangover may occur as effects begin to wear off.

EFFECTS OF SHORT-TERM USE: MODERATE DOSES[2]

Low-dose effects tend to become more intense. The following effects may also occur at moderate dose levels:

CNS, behavioral, subjective: induction of sleep. Prior to the onset of sleep, or when sleep does not occur, a state similar to mild alcohol or barbiturate intoxication is often manifested and can be characterized by mild euphoria, mild impairment of cognitive, perceptual, and motor functions, mild emotional disinhibition, sometimes slurred speech and mood swings, and on rare occasions paradoxical excitement.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

Effects of low to moderate doses tend to become more intense. The following effects may also occur at higher dose levels:

CNS, behavioral, subjective: Induction of deep sleep is the most probable effect; however, prior to the onset of sleep, or when sleep does not occur, the clinical picture resembles moderate- to high-dose

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[1] Single doses between 125 and 250 mg taken orally by nontolerant users.

[2] Single doses of 500 mg taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

[3] Single doses of more than 500 mg taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

> alcohol or barbiturate intoxication. As the size of the dose increases, cognitive, perceptual, and motor functions are increasingly impaired. The impairments are principally manifested as oversedation or a brief period of increased activity; concentration difficulties; impairment of short-term memory; increasingly intense euphoria, or emotional depression or hostility, or mood swings; impairment of fine and gross motor coordination; and impaired judgment.

Cardiovascular: rapid heart rate; drop in blood pressure.

At very high doses (i.e., sufficient to produce coma), glutethimide can produce the following effects: drop in body temperature followed by fever; abnormally rapid heart rate, abnormally low blood pressure; exaggerated reflexes; intermittent muscle spasms, twitching of the facial muscles; and dilated pupils. Seizures have also been reported occasionally to occur after the ingestion of very high nonlethal doses. Respiratory depression can occur, but is generally much less severe than for overdose of barbiturates.

EFFECTS OF LONG-TERM USE

As with most other sedative/hypnotic drugs which induce sleep, glutethimide adversely affects normal sleep processes. Glutethimide substantially suppresses REM (rapid eye movement) sleep, those recurring phases of sleep characterized by constant oscillation of the eyeballs, constant dreaming, and extreme muscle relaxation. Reduced REM sleep can have deleterious psychological consequences, which can range from mild daytime restlessness to psychotic episodes in extreme cases. Termination of use of sedative/hypnotics to induce sleep can produce a REM rebound; that is, the amount of sleep time devoted to REM sleep temporarily exceeds normal. Researchers believe that this phenomenon is a form of physical withdrawal.[4]

With chronic use, there is a risk of accumulation of glutethimide in the body.[5] Therefore, some long-term users may experience a continuation of certain short-term effects, such as motor incoordination and unsteadiness, muscle weakness, visual difficulties, thinking and memory impairment, and slurring of speech, as well as tremors, irritability, and apathy. When glutethimide is chronically abused at high doses, these symptoms are often quite severe. Sometimes, chronic intoxication can result in such extreme consequences as toxic psychosis, manifested as delirium and hallucinations.

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[4] For further discussion of REM sleep, see the chapter Sedative/Hypnotics in section 2.

[5] Particularly in liver-diseased or elderly patients.

Some users taking daily doses of 500 mg of glutethimide or higher experience withdrawal symptoms identical to those shown by physically dependent users upon abrupt abstinence. The symptoms apparently spontaneously occur in those users even though they are still taking the drug. (The withdrawal syndrome is described below under Tolerance and Dependence.)

Chronic users of glutethimide often suffer insomnia and poor sleep after tolerance develops, and consequently are subject to daytime lethargy and fatigue.

LETHALITY

Severe overdose is characterized by prolonged coma, very high body temperature, very low blood pressure, and depression of vital signs. There is a depression or absence of deep tendon reflexes, pupillary response, and response to painful stimuli. Pupils are fixed and maximally dilated. Serious respiratory complications often occur; however, depression of the respiratory control centres in the brain is not as severe as with barbiturate overdose. Convulsions occasionally occur. Death is usually attributed to cardiovascular collapse or to respiratory complications. Generally, overdoses of 10–20 grams (10,000–20,000 mg) produce lethal results. When taken in combination with other CNS depressants, lower doses can be lethal.

TOLERANCE AND DEPENDENCE

Tolerance

With nightly use, tolerance develops rapidly to the sleep-inducing effects of glutethimide, typically within a few weeks. Tolerance also develops rapidly to the sedative and euphoric effects when this drug is regularly used. If the user wishes to maintain the original intensity of any of these desired effects, the size of the daily dose must be increased. Abusers therefore tend to increase their daily dose on several occasions.

There is a high degree of cross-tolerance between glutethimide and such other sedative/hypnotic drugs as alcohol and the barbiturates: that is, once tolerant to a given effect produced by glutethimide, the user will also be tolerant to the same effect produced by an equivalent dose of these other drugs.

Psychological and Physical Dependence/Withdrawal

Psychological dependence on glutethimide can occur irrespective of the size of the daily dose and even when the drug is not taken on a daily basis. Psychologically dependent users have acquired a craving for the psychological effects such that the drug takes on a magnified importance in their daily life. They are likely to be preoccupied with procuring an adequate supply, and if the drug is temporarily unavailable to them, anxiety or even feelings of panic may ensue.

Physical dependence on glutethimide develops when the drug is chronically administered at doses as small as three to four times the typical daily therapeutic dose. When even higher daily doses are taken for protracted periods (such as several months), an extremely severe withdrawal sickness results upon abrupt cessation of use. Early withdrawal symptoms tend to occur within 24 hours after the last dose and may include sweating and fever alternating with chills; nausea and vomiting; abdominal cramps; abnormally rapid heart rate; headache; tremors, muscle twitches, and spasms; agitation and hyperactivity; insomnia, or brief periods of agitated sleep accompanied by nightmares; uncontrollable facial grimaces; psychosis characterized by disorientation, delirium, hallucinations, and paranoid delusions; and grand mal seizures. When withdrawal has been undergone without medical treatment, severe uninterrupted seizure activity has occurred and has been reported as resulting in a number of deaths. As noted earlier, many of these symptoms, including grand mal seizures, have abruptly occurred in some regular glutethimide users without their abstaining from the drug. The causes of this phenomenon are not understood.

Because of the substantial degree of cross-dependence between glutethimide and the barbiturates, phenobarbital has been used in medical settings to mitigate the severity of glutethimide withdrawal sickness. Initially, phenobarbital is administered in high daily doses, and then the size of the daily dose is gradually reduced. This procedure lessens the probability of occurrence of the more hazardous features of the glutethimide withdrawal syndrome.

PATTERNS OF USE

Within a few years after its introduction in 1954, glutethimide came to be widely abused in spite of its known propensity for producing hazardous consequences at high doses. Many drug abusers often took glutethimide in combination with such other CNS depressants as alcohol, barbiturates, and narcotic analgesics; these combinations resulted in a number of overdose deaths. Many deaths also resulted when glutethimide alone was taken in large quantities.

Medical use of glutethimide seems to have declined during the past decade, and it is now only infrequently encountered on the street drug market. It is difficult to explain its continued medical use, for its risks are known and it offers no special advantages over other currently available products (Harvey, 1980).

ABUSE POTENTIAL

Dependence Liability

Taken orally, glutethimide is rapidly absorbed from the gastrointestinal tract into the bloodstream. Its effects are usually perceptible within 15–20 minutes after ingestion. The degree of pleasurable intoxication produced by this drug is similar to that of the barbiturates. Therefore, its dependence liability appears to be as great as that of the short-acting barbiturates such as secobarbital and pentobarbital.

Inherent Harmfulness

When abused in acute high doses or over protracted periods of time, glutethimide is at least as dangerous as the barbiturates. In fact, if taken regularly, even at therapeutic dose levels, it can have serious repercussions for the medical user including the abrupt onset of withdrawal-like symptoms during the course of therapy.

Availability

Because there has been a decline in the prescribing of glutethimide, the abuse potential is not as great as it was in the past.

REFERENCE

Harvey, S.C., Hypnotics and sedatives, in *The Pharmacological Basis of Therapeutics*, A.G. Gilman, L.S. Goodman, and A. Gilman (Eds.), 6th ed., 339-375, Macmillan, New York, 1980.

Heroin

DRUG CLASS: NARCOTIC ANALGESIC;
OPIATE

SYNOPSIS

Heroin is a powerful semisynthetic narcotic analgesic produced by chemical modification of morphine. Because of the potency of its euphoric and analgesic effects, heroin has the greatest potential for producing dependence of any of the common narcotic analgesics. Although the drug can be administered by several routes—injected, sniffed, smoked, or swallowed—North American heroin-dependent users prefer to inject it intravenously ("mainlining"); this results in the desired effects being both more immediate and more intense than with administration by any other route. However, most inexperienced users in their initial encounters with heroin either inhale it through the nasal passages ("snorting") or inject it subcutaneously ("skin popping"). In many instances these early experiences are unpleasant: nausea and vomiting are quite common. Generally the desired effects are only fully appreciated after the user acquires tolerance to these early adverse effects; however, tolerance to such desired effects as euphoria, tranquility, and analgesia can also develop rapidly. To compensate for tolerance, or to achieve more intense pleasurable effects, fledgling users must increase their daily dose and change their route of administration, both of which increase the risk of dependency. Although severely distressing, the withdrawal sickness after abrupt termination of heroin use is rarely fatal. In many respects, it resembles a case of moderately severe flu, and most observable symptoms disappear within seven to 10 days. The principal cause of death from heroin overdose is cessation of breathing (respiratory arrest), the result of severe depression of those brain centres which control breathing.

DRUG SOURCE

Heroin is a semisynthetic drug produced through chemical modification of the natural alkaloid morphine by exposing the latter to acetic acid. Heroin is produced under special licence in very small quantities for research purposes, and in Great Britain for carefully monitored heroin maintenance programs for treating heroin-dependent persons. Street heroin is produced in illicit laboratories.

TRADE NAMES

Not applicable.

STREET NAMES

Dust, "H," horse, junk, smack, scag.

COMBINATION PRODUCTS

Heroin is sometimes encountered on the illicit market in combination with amphetamines (bombitas) or with cocaine (dynamite, speedball, whizbang).

MEDICAL USES

Heroin was formerly employed in North America as a powerful analgesic, but because of its high dependence liability it has now been completely replaced by other narcotic analgesics. In some countries, it is still used in controlling the pain of advanced cancer. As noted above, it continues to be used in Great Britain in heroin maintenance programs.

PHYSICAL APPEARANCE

In pure form heroin is a fine white crystalline powder with a bitter taste, soluble in water. It is diluted for sale on the illicit market with a variety of substances such as milk sugar, dextrose, or quinine. Heroin from certain parts of Asia and Mexico is brown in color because of the impurities present.

DOSAGE

Medical

When used for relief of pain, usually 1–8 mg injected subcutaneously.[1]

[1] Heroin's analgesic potency is approximately three times greater than morphine's.

Nonmedical

Inexperienced users may be introduced to the drug at dosages of 2–3 mg or less. Some dependent users claim to take as much as 200–300 mg per day.

HEROIN USERS' ESTIMATES

Whether heroin-dependent persons use as much as they believe they do is open to question; most of them probably overestimate the amount they take. The content of heroin in a typical "street bag" (judged from seizures and samples confiscated by the authorities) varies considerably; in many instances the heroin constitutes less than 10%, and often less than 5%, of the total weight. Purity of 20% or more at the street level is infrequent. The remainder of the product may include inactive diluents, most commonly the sugars lactose or dextrose, and substitutes such as quinine which are added to contribute to a bitter taste suggestive of a high-potency product. The street heroin-dependent user, having no way to reliably estimate the amount of heroin in a bag when making a purchase, is vulnerable to being cheated ("burned"). However, a number of North American users have, in the past, developed personal connections through which they receive their own supplies of heroin directly from Asia; such "direct purchase" supplies are often of exceptionally high purity (e.g., greater than 80% heroin).

ROUTES OF ADMINISTRATION

Most commonly the powder is dissolved in water and injected subcutaneously, intramuscularly, or intravenously. The intravenous route ("mainlining") is generally preferred, as it produces the most rapid and intense response to the drug.[2] Occasionally heroin is sniffed or taken orally.[3] (However, oral consumption is not the route of choice for dependent users, for directly after heroin is absorbed from the small intestine, it must pass through the liver, where it is rapidly destroyed. Much of the drug is thus wasted.) Smoking heroin was reported to be a very common event for soldiers in Vietnam, where the drug was relatively freely available and inexpensive by Western standards. Heroin has also been smoked in combination with regular cigarettes or marijuana. When smoked, its effects are more potent than those of smoked opium.

[2] Heroin produces a more intense "rush" than the same intravenous dose of morphine, apparently because the greater fat solubility of heroin enables it to penetrate the brain more rapidly than morphine. Once in the brain, heroin is rapidly metabolized to morphine; possibly this conversion is necessary for it to produce its effects.

[3] When taken orally heroin may be put into bread or even small twists of tissue paper to mask its bitter taste.

EFFECTS OF SHORT-TERM USE: LOW DOSES[4]

CNS, behavioral, subjective: suppression of the sensation of pain; euphoria, mental clouding, heightened feelings of well-being; relaxation and drowsiness in some, and in others garrulousness and activity. Shortly after administration the user may experience a drowsy, dreamy, mild dozing state referred to as a "nod" (owing to the characteristic lolling of the head). Often there is decreased physical activity, inability to concentrate, apathy, pupillary constriction, droopy eyelids, reduced visual acuity, and impairment of night vision. Inexperienced users may react with giddiness and dizziness or fearfulness and anxiety. Often several repetitions with the drug, usually with the encouragement of peers, may be necessary before the above desired effects are fully recognized.

Cardiovascular: slightly lowered body temperature, sweating.

Respiratory: slightly slowed respiratory rate.

Gastrointestinal: nausea and vomiting (very common among inexperienced users); reduced appetite; decreased gastric motility and constipation.

Other: reduced libido; itching or burning sensation on the skin; increased urinary output.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[5]

Intensification of low-dose effects may occur. The duration of effects increases with increased dosage. As the dose increases, sensitivity and emotional response to painful stimuli decrease; ability to concentrate is increasingly impaired; there is a greater probability of sleep; breathing becomes progressively slower and more shallow; and heart rate gradually slows and blood pressure decreases.

The most desired effect is referred to as a "rush." It occurs almost immediately following intravenous injection, and the subjective experience has been described as akin to an intense orgasmic sensation in the abdomen.

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[4] Single 3–4 mg dose taken by injection in nontolerant persons.

[5] Single dose of 10–25 mg or higher by injection in nontolerant users, or lower doses in particularly sensitive individuals.

In very high doses (i.e., overdose) heroin can produce deep sleep possibly progressing to stupor or coma, low blood pressure, slow and irregular heart rate, cyanosis, shallow and marked depression of respiration, low body temperature, flaccidity of skeletal muscles, cold and clammy skin, and pinpoint pupils.

EFFECTS OF LONG-TERM USE

When heroin- (and morphine-)dependent persons have been provided with daily maintenance doses under medical supervision, marked physiological deterioration or significant psychological impairment has not been observed. In fact, most of the serious adverse consequences of chronic heroin use are generally related to lifestyle and factors involving needle administration. Those adverse consequences that are directly related to long-term heroin use are similar to those produced by other narcotic analgesics: mood instability due to the relatively short action of the drug, reduced libido, constipation, pupillary constriction (which adversely affects night vision), menstrual irregularity, and certain types of respiratory impairment.

LIFESTYLE AND CHRONIC NEEDLE ADMINISTRATION

Infections at injection sites and collapsed veins resulting from repeated injections are very common. Tetanus, viral hepatitis (which is reported in New York City to be among the most common causes of admission of heroin addicts to hospital medical services), endocarditis,[6] pneumonia, and other pulmonary complications including tuberculosis all have a significantly higher incidence among heroin addicts than among the general population. While there is no evidence of permanent CNS impairment specifically due to chronic heroin use, diminished oxygen intake resulting from a nonlethal overdose may result in brain damage. Malnutrition, poor housing, untreated illness, and frequent use of and dependence on other addictive drugs in conjunction with heroin dependence tend to result in a generally poor state of health and lowered resistance to disease.

LETHALITY

Severe overdose, usually self-administered and unintentional, results in very slow, shallow, and irregular respiration, flushing, pinpoint pupils, cyanosis, markedly decreased blood pressure, and coma. Administration of a narcotic antagonist[7] which can reverse the acute effects of overdose of heroin (or other opiates and opioids) is an essential part of the emergency treatment under these conditions. Death, when it occurs, usually results from respiratory arrest or other respiratory or cardiovascular complications.

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[6] Infection of the membrane lining of the interior of the heart.

DEATHS FROM OTHER CAUSES

While heroin overdose is the most frequently reported cause of death among heroin addicts, a substantial number of deaths can also be linked to their characteristic lifestyle. In one recent study concerning the causes of death of 1,400 addicts, it was estimated that up to 40% may have been caused by violence, usually murder. Suicide and deaths from infectious diseases are reported to have a considerably higher incidence than in the general population.

TOLERANCE AND DEPENDENCE

Tolerance

Profound tolerance to most of the effects of heroin develops rapidly with regular use. But it is less likely to develop with infrequent or intermittent use at lower doses and by routes of administration other than intravenous (see "chippying" below). Increasingly higher doses are required to produce satisfactory analgesic, sedative, and euphoric effects; tolerance also develops to its respiratory-depressant and nausea-inducing effects. However, tolerance has not been reported to develop to the pupillary-constricting or constipating effects.

As tolerance develops with chronic use, and the user gradually increases the dose to achieve the desired effects, a dose plateau is reached where no amount of the drug is sufficient to produce the intensity of effects desired. When this level is achieved, dependent users continue to administer the drug, but now almost exclusively for the purpose of delaying withdrawal sickness, which characteristically commences between 8 and 12 hours after the last dose.

Physical Dependence/Withdrawal

Powerful physical and psychological dependence also can occur very rapidly for the regular high-dose user. The severity of withdrawal sickness, which follows abrupt cessation of use, is related to several factors: how long the individual has regularly used the drug and at what dosage, general health, and the conditions under which withdrawal occurs.

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[7] See Naloxone article below.

Early Symptoms: With onset typically between 8 and 12 hours after the last dose, symptoms include watering eyes, discharge of nasal mucus, yawning, and sweating. This stage is characteristically followed by a phase referred to as the "yen"—an agitated sleep which may last for several hours. Upon wakening, agitation continues, accompanied by depression, loss of appetite, gooseflesh, dilated pupils, and tremor.

Peak Intensity: The peak generally occurs between 36 and 72 hours after the last administration. Usually there are alternations between bouts of chills and shivering and bouts of flushing and excessive sweating. Gooseflesh is highly prominent.[8] Other observable symptoms during the peak period include increased irritability, insomnia, continued loss of appetite, violent yawning and sneezing, continued watering of the eyes and nasal discharge, vomiting, nausea, intestinal spasms, diarrhea, elevated heart rate and blood pressure, abdominal cramps, pains in the bones and muscles, muscle spasms, and uncontrolled kicking movements.[9] General weakness, increasingly severe agitation, and emotional depression also occur.

Secondary effects, resulting from not taking food or fluids (combined with vomiting, sweating, and diarrhea), include weight loss, dehydration, and disturbance of the acid/base balance.

Severity of the syndrome gradually declines, and most observable symptoms are no longer present within 7 to 10 days after the onset of withdrawal sickness.

At any point during the course of withdrawal sickness, even at its peak, administration of a suitable amount of heroin or most other narcotic analgesics[10] will quickly result in the complete disappearance of

[8] The skin is reported to resemble that of a plucked turkey—hence, probably, the expression "cold turkey" for abrupt cessation of drug use by physically dependent users.

[9] It has been suggested that the expression "kicking the habit" is derived from these muscle spasms and uncontrolled kicking movements.

[10] It is usually impractical to use low-potency drugs such as codeine and propoxyphene to suppress heroin withdrawal, for they have serious side effects at very high doses.

the syndrome. That narcotic analgesics other than heroin have the ability to partially or completely (depending on the amount of the dose) suppress heroin withdrawal is an example of a more general principle of cross-dependence among narcotic analgesic drugs.[11]

"CHIPPYING" (OR "CHIPPING")

It is popularly believed that even occasional use of heroin will inevitably lead to dependence as described above. Indeed, the vast majority of heroin addicts are likely to have commenced drug use on an intermittent basis, deceiving themselves into believing that physical dependence would not happen to them. However, not all heroin users develop a significant tolerance to or become physically dependent on the drug. Some heroin users seem to be able to engage in "chippying," using the drug infrequently or on a regular intermittent basis, such as only on weekends, without inevitably increasing the dose or frequency of use. However, it should be kept in mind that virtually all physically dependent heroin users once believed that they could continue to use heroin in this manner indefinitely without escalating the dose or frequency of use.

Psychological Dependence

Long after the observable physical components of withdrawal sickness are completed, and in spite of continuing medical and psychological intervention, the residue of the profound impact of heroin addiction can persist. Chronic depression, anxiety, insomnia, loss of appetite, periods of agitation, and a continued craving for the drug may last for extended intervals of time. Out of all drugs of abuse, recidivism (reengaging in drug use) is among the highest in those who have tried to stop the use of narcotic analgesics; even among those taking medically supervised methadone many still report a craving for heroin, although for them recidivism is considerably lower.

Such symptoms are often reported to be indicative of psychological dependence. However, a purely psychological explanation may be an oversimplification. Much is yet to be understood about possibly complex physiological adjustments which may result from narcotic analgesic dependence and the fate of these adjustments after withdrawal.

PATTERNS OF USE

While heroin-dependent people come from all walks of life, it has long been recognized that the highest concentration of regular users in North America tends to be in the central areas of large cities. Although some generalizations about the typical progression and characteristics of users can be made, they should be interpreted with considerable caution, for they by no means apply to all heroin-dependent people.

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[11] In fact, an individual tolerant to an effect of one opiate or opioid will also be cross-tolerant to this effect in other drugs of this class.

A disproportionately high number of those who become heroin dependent are male and drawn from lower socioeconomic and disadvantaged minority groups. First-time users tend to be young (in their teens); usually they have had at least some (and, in many instances, considerable) experience with other drugs of abuse; they are likely to associate with other drug users, among whom some have at least occasionally used heroin or other narcotic analgesics; often there has been considerable family disorganization; and both performance and interest in school are low.

The first experience with heroin often results from both curiosity and peer-group pressure. Early and irregular intake experiences are usually through "snorting" (nasal inhalation) or "skin-popping" (subcutaneous injection). Graduation to intramuscular or intravenous injection tends to result from the desire to achieve a quicker and more intense "high." As well, it may be an early sign of increasing tolerance to and dependence on the drug. With each progressive step—increasing the dosage, using a more direct route of administration, and increasing the frequency of administration—the risk of dependence increases. Ultimately, the overwhelming majority of those who proceed to "mainlining" (intravenous injection), which results in the most rapid and intense pleasurable response, can be viewed as having achieved a highly significant degree of both physical and psychological dependence.

Maintaining and supporting heroin addiction can be very expensive; and enormous fluctuations in cost can occur literally overnight and without any notice. In conformance with the laws of street-drug supply and demand, a major drug "bust" (police seizure) can result in a dramatic increase in the price.

"Polydrug" abuse (concurrent abuse of more than one drug) is remarkably high among heroin-dependent persons. Barbiturates and other sedative/hypnotics such as alcohol are reported to be widely abused. Barbiturates can produce a pleasurable state of intoxication in those who have achieved a level of tolerance to heroin so great that they can no longer experience even a mild "high" from it.[12] However, neither barbiturates nor other sedative/hypnotics can delay or reduce the intensity of heroin withdrawal sickness. Stimulants such as amphetamines and cocaine have also been commonly used. In fact, some researchers have suggested that many heroin-dependent persons were among the vanguard when cocaine reemerged in the 1960s as a popular drug of abuse after several decades of obscurity.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of heroin is the greatest of any of the narcotic analgesics in common use including morphine. This characteristic results from both its extremely powerful euphoric and analgesic effects and its solubility. The high fat solubility of heroin permits immediate and intense gratification, since the drug enters the brain extremely rapidly after intravenous injection.

Inherent Harmfulness

In low to moderate doses, the adverse effects of heroin are relatively mild (e.g., nausea and vomiting) and frequently not sufficiently distressing to persuade the inexperienced user to discontinue taking the drug. Higher doses of heroin—generally in amounts much greater than that to which the user has developed tolerance—can, however, be life-threatening, especially in the case of street users, who cannot be sure of the size of the dose they are injecting. Nevertheless, because of the powerful dependence-producing properties of heroin, and often in spite of firsthand knowledge of deaths from overdose, street users must accept this risk.

Availability

In the past, when heroin was employed in North America in clinical medicine, the drug was widely abused. Nowadays, possession and manufacture of heroin are illegal in Canada, the United States, and most other countries, and there is a concerted international effort to prevent its illicit manufacture and distribution. Therefore, its current potential for widespread abuse is greatly restricted by lack of availability and by the attendant legal, social (except within the street-drug subculture), and moral sanctions.

[12] Combining heroin and such CNS depressants as barbiturates is a practice which can prove fatal, as both present a risk of significantly depressed respiration, and the combination can result in death from respiratory arrest.

Hydromorphone

DRUG CLASS: NARCOTIC ANALGESIC; OPIATE

SYNOPSIS

Hydromorphone (dihydromorphinone) is a powerful semisynthetic narcotic analgesic. Its primary clinical uses are in relief of severe pain and suppression of severe cough. When it is administered by subcutaneous injection (the most common medical route of injection), its analgesic potency is estimated to be seven to eight times greater than that of morphine. In low doses, the side effects of hydromorphone such as nausea, vomiting, and drowsiness are both less common and milder than for most other powerful drugs in its class; however, because of its powerful depressant effect on the centres of the brain controlling respiration, a lethal dose of hydromorphone is smaller than a lethal dose of most of these other drugs.

Tolerance to the effects of hydromorphone tends to develop gradually; nevertheless, powerful physical dependence can rapidly develop with high-dose abuse. The withdrawal syndrome after abrupt abstinence is similar to but less severe than that produced after abrupt abstinence from heroin or morphine—i.e., with symptoms resembling those produced by a case of moderately severe flu.

The euphoric potency of hydromorphone is lower than that of most other powerful narcotic analgesics, and when chronically injected it also produces more pain and tissue irritation. However, because of its relatively easy availability in prescription cough syrup and its low cost when compared to street-purchased narcotic analgesics, hydromorphone has recently achieved popularity among abusers.

DRUG SOURCE

Hydromorphone is a semisynthetic drug produced by the pharmaceutical industry through chemical modification of morphine.

TRADE NAMES

Dilaudid. It is also marketed under its nonproprietary name.

STREET NAMES

"Juice" (a common street name for all cough syrups containing narcotic analgesics); dillies.

COMBINATION PRODUCT

Dilaudid cough syrup (hydromorphone, glyceryl, guaiacolate, and alcohol 5%).

MEDICAL USES

- moderately severe and severe pain;
- suppression of severe cough.

PHYSICAL APPEARANCE

In pure form hydromorphone occurs as a fine white odorless crystalline powder which is soluble in water and slightly soluble in alcohol.

DOSAGE

Medical

- for pain—2–4 mg every 4 to 6 hours orally or by subcutaneous or intramuscular injection;
- for cough—1 mg in 5 ml solution every three to four hours.

Nonmedical

Doses of up to 100 mg per day have been known. It has also been reported that a dose one-seventh that of morphine (by weight) can effectively sustain severe morphine dependence.

ROUTES OF ADMINISTRATION

Orally in solution or tablet form; also by subcutaneous, intramuscular, or intravenous injection, and by rectal suppository.

EFFECTS OF SHORT-TERM USE: LOW DOSES[1]

CNS, behavioral, subjective: suppression of the sensation of and emotional response to pain,[2] mild euphoria; drowsiness (occasionally), lethargy, relaxation, difficulty in concentrating, lightheadedness; mild anxiety or fearfulness; suppression of cough reflex; pain at the site of injection (due to hydromorphone's local-tissue irritating properties when injected). Pupillary constriction does not occur.

Cardiovascular: slight drop in body temperature, sweating.

Respiratory: slightly reduced respiratory rate.

Gastrointestinal: mild nausea, vomiting, suppression of appetite, and constipation.

Other: reduced libido.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

Intensification of low-dose effects may occur. Duration of effects increases with increased dosage. As the dose increases:

1. Sensitivity and emotional response to painful stimuli decrease.
2. There is a greater probability of sleep.
3. Ability to concentrate is increasingly impaired.
4. Breathing becomes progressively slower and more shallow.
5. Heart rate gradually slows and blood pressure decreases.
6. The degree of euphoria produced increases, but is not as intense as that produced by morphine or heroin.

In very high doses (i.e., overdose) hydromorphone can produce deep sleep which may progress to stupor or coma, low blood pressure, slow heart rate, cyanosis, shallow and markedly reduced rate of breathing, low body temperature, flaccidity of skeletal muscles, and cold and clammy skin.

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[1] Single doses of 2–4 mg taken either orally or by subcutaneous or intramuscular injection in nontolerant persons, up to 20 mg per day.

[2] Hydromorphone's analgesic potency is seven to eight times greater than morphine's.

[3] Single doses above the therapeutic range administered either orally or by injection in nontolerant persons.

EFFECTS OF LONG-TERM USE

Chronic subcutaneous injection of hydromorphone in one area tends to produce more pronounced pain, tissue irritation, and hardening of the tissue under the skin than do most other common narcotic analgesics; however, other effects are similar to those produced by other drugs in this class. Apart from the above, there is no evidence of marked physiological deterioration or significant psychological impairment resulting from long-term use of hydromorphone.

Other adverse consequences directly related to chronic hydromorphone use include mood instability,[4] constipation, reduced libido, menstrual irregularity, and certain types of respiratory impairment.

LETHALITY

Because of the potency of hydromorphone's respiratory-depressant effect, an overdose that can be lethal to a nontolerant individual is smaller than is the case for most other narcotic analgesics; it is estimated to be approximately 100 mg. Severe overdose results in coma, cessation of breathing, circulatory collapse, cardiac arrest, and death.

TOLERANCE AND DEPENDENCE

Tolerance

Generally, tolerance to the main effects of hydromorphone develops more gradually than with most other potent narcotic analgesics; however, tolerance to the euphoric, sedative, analgesic, and respiratory-depressant effects clearly does develop. As with many other narcotic analgesics, as tolerance develops with chronic use and the user gradually increases the dose to achieve the desired effects, a dose plateau is reached where no increase in the size of the dose is capable of producing the intensity of effects desired; attempts to go above that plateau can be lethal because of hydromorphone's pronounced respiratory-depressant effect at higher doses. The dependent user continues to

[4] Mood instability is due to the relatively short duration of action of hydromorphone. The effects of a therapeutic dose last for approximately four hours.

administer the drug with the same frequency and dose, but now almost exclusively to prevent withdrawal sickness.

Physical Dependence/Withdrawal

After long-term administration of hydromorphone, abrupt cessation of use or abrupt reduction of the dose to substantially below that to which the user is tolerant will result in withdrawal sickness of the morphine type. Early symptoms may appear as briefly as three hours after the last dose, but while they are qualitatively similar to those produced by morphine or heroin withdrawal, they tend to be less severe.

In chronic high-dose users, early withdrawal symptoms include exaggerated autonomic responses (e.g., rapid heart rate), runny nose, anxiety, gooseflesh, tremor, yawning, insomnia, temperature elevation, watering eyes, and restlessness. Later withdrawal symptoms include vomiting, convulsions (rarely), diarrhea, severe abdominal pains, loss of appetite, elevated heart rate and blood pressure, severe agitation, insomnia, pains in the muscles and joints, muscle spasms, and uncontrolled kicking movements.

The severity of the syndrome gradually declines, and most observable symptoms disappear within approximately seven days.

Psychological Dependence

The profound impact of long-term dependence on hydromorphone (and other narcotic analgesics) is often observable for extended periods of time after the classical phase of withdrawal sickness has been completed. Depression, anxiety, insomnia, loss of appetite, periods of agitation, and a craving for the drug may persist for a long time. Such symptoms are often reported to be indicative of psychological dependence. However, an explanation based purely on psychological factors may be an oversimplification. Much is yet to be understood about the possibly complex physiological adjustments which may result from narcotic analgesic dependence and the fate of these adjustments after withdrawal.

PATTERNS OF USE

Because hydromorphone is among the greatest in analgesic potency of all of the common narcotic analgesics,[5] it is employed in hospitals for cases of extreme pain. Furthermore, because of its powerful suppressant effect on the cough reflex, hydromorphone has proven to be effective in the management of severe cough.

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[5] Of the narcotic analgesics in common use, only oxymorphone (e.g., Numorphan) possesses greater analgesic potency than hydromorphone.

Until the past decade, hydromorphone did not appear to be widely popular among street narcotic analgesic abusers. However, a recent trend suggests that hydromorphone (in the form of cough syrup and tablets) has gained considerable favor, and it is now generally agreed to have become an important drug of abuse; in fact, many narcotic analgesic abusers who formerly were injecting drugs in this class have switched to oral consumption of hydromorphone (in tablets or cough syrup), hydrocodone (in cough syrup, e.g., Novahistex DH), and oxycodone (e.g., Percodan tablets).

Street abusers obtain hydromorphone either by theft from pharmacies, by forging prescriptions on stolen prescription blanks, or by faking symptoms of severe cough and respiratory congestion so as to obtain prescriptions from sympathetic physicians. It is not unusual for a hydromorphone abuser to obtain several prescriptions per week from different doctors.

ABUSE POTENTIAL

Dependence Liability

Although hydromorphone has powerful analgesic properties, researchers report that when it is injected its euphoric effects are not as intense as those of other powerful drugs in this class such as morphine and heroin. When it is taken orally, the intensity of its euphoric effects is further diminished; in comparison to injection routes the oral route requires a longer period of time for the drug to reach the target sites in the brain.

Inherent Harmfulness

Chronic injection of hydromorphone produces greater tissue irritation and pain than do most other narcotic analgesics. Therefore, the various routes of injection tend in the long run to be less preferable than oral administration.

Because of its highly potent effect on brain centres controlling respiration, lethal doses are usually lower than for most other narcotic analgesics.

Availability

The key variables related to hydromorphone's current popularity appear to be its relatively easy availability, its relatively inexpensive cost, and (unlike street-purchased narcotic analgesics) its high degree of consistent purity. In addition, dependence on a drug such as hydromorphone does not carry the same social stigma as heroin dependence. For these reasons, regular users of hydromorphone appear to be willing to forgo the more immediate and intense effects of injected narcotic analgesics.

Inhalants

DRUG CLASS: SEDATIVE/HYPNOTICS; ANESTHETICS

SYNOPSIS

Almost all commonly abused inhalants are volatile hydrocarbon solvents produced from petroleum and natural gas[1]—"volatile" meaning that they evaporate when exposed to air, and "solvents" referring to their capacity, in liquid form, to dissolve many other substances. Volatile hydrocarbons have an enormous number of industrial, commercial, and household uses: for example, automobile fuels, cleaning fluids, toiletries, adhesives and fillers, and paint thinners and paints. Certain ones have been used as pressurized propellants in aerosols and as anesthetics. Frequently, two or more volatile hydrocarbon compounds are found in the same product.

Inhalants generally produce a number of dose-related central nervous system (CNS) depressant effects similar to those of other sedative/hypnotic substances. However, while small doses of inhalants can produce alcohol-like intoxication, they also tend to produce temporary sensory and perceptual distortions, often accompanied by delusions of grandeur. The latter effects may give rise to bizarre behavior which can be injurious to the user and to others. At progressively higher dose levels, inhalants produce sleep and anesthesia.

Tolerance develops to the desired effects of inhalants, and psychological dependence frequently occurs. However, it is uncertain whether chronic abuse of these substances results in physical dependence; when abrupt termination of inhalant abuse does produce withdrawal sickness, the symptoms are usually mild, although in some cases delirium tremens and other severe symptoms have occurred.

There have been a number of deaths associated with acute abuse of inhalants, most prominently "sudden sniffing deaths" and suffocations. Sudden sniffing death is caused by heart failure resulting from severely irregular heartbeat; the heart irregularity is typically preceded

[1] Two principal exceptions are amyl nitrite and nitrous oxide.

by strenuous activity or abrupt stress immediately following several deep inhalations. In the case of suffocation, death is a result of the person's falling asleep or otherwise becoming unconscious while a plastic bag containing the inhalant remains in place over the nose and mouth. Chronic abuse of inhalants can produce a spectrum of different harmful effects depending on the particular inhalant; these effects can range from relatively mild and reversible symptoms to severe damage to such vital organs as the kidneys and liver.

The article will be divided into two sections in order to distinguish some important differences in effects (particularly in lethality) between the widely abused solvents employed in industrial and commercial products and those solvents which in the recent past were used as aerosol propellants. A table at the end of the article lists and classifies most of those solvents that either were or still are subject to abuse.

INDUSTRIAL AND COMMERCIAL SOLVENTS:

DRUG SOURCE

The most commonly abused industrial and commercial solvents are volatile hydrocarbon compounds produced from petroleum and natural gas through chemical synthesis by the chemical industry.

TRADE NAMES

None of the commonly abused substances in this group has any medical use.

STREET NAMES

Glue, gas, and sniff.

COMBINATION PRODUCTS

The following are among the most commonly abused products. Only their pharmacologically active constituents are listed.

1. Cleaning fluid (spot remover or shoe polish): carbon tetrachloride (no longer in use), naphtha, perchlorethylene, trichloroethane, trichloroethylene.

2. Nail polish remover: acetone, aliphatic acetates, benzene.[2]
3. Gasoline: toluene, naphtha, and several other solvents.
4. Household cements: acetone, methyl ethyl ketone, methyl isobutyl ketone, toluene.
5. Lacquer thinners: aliphatic acetates, toluene.
6. Lighter fluid: naphtha.
7. Model cements, airplane glue: acetone, toluene.
8. Plastic (styrene) cements: acetone, aliphatic acetates, benzene, cyclohexane, n-hexane, toluene, trichloroethylene.
9. Rubber tire patching cement: benzene, hexane, trichloroethylene.

Other products containing solvents of abuse include paint and varnish removers, paint brush cleaners, household waxes, typewriter correcting fluids and thinners, general household cleaners, floor wax removers, degreasers, and suede cleaners.

DOSAGE

Medical

No medical use.

Nonmedical

With so many different substances in different concentrations and in differing combinations in various products, it is not possible to accurately document the dosages necessary to produce a desired level of intoxication. A single container of cleaning fluid or nail polish remover may be sufficient for a group of young abusers. A frequent and very heavy abuser of model cement (airplane glue) may use as many as a dozen tubes of glue in order to maintain a continued period of intoxication. The concentration of toluene when used specifically for the purpose of promoting intoxication may exceed by fiftyfold the maximum atmospheric concentration that is legally permitted in an industrial setting (i.e., 200 parts per million).

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[2] Benzene is no longer in use in most industrial products or in any household products.

ROUTES OF ADMINISTRATION

Volatile solvents are almost always inhaled. There is a variety of methods (Barnes, 1979):

1. One of the most common methods for inhaling semiliquid solvents involves emptying the contents of the container into a plastic or paper bag and holding its opening tightly and firmly over the mouth and nose; the vapors are then deeply inhaled.[3]
2. When liquid solvents are used, they may be sniffed directly from the container.
3. Liquid solvents may also be poured onto a rag or some other absorbent material; the saturated material is then held in the hands and cupped over the mouth or placed in a bag and then inhaled.
4. Sometimes solvents are heated in order to achieve higher vapor concentrations.
5. Some other less common methods involve the use of such items as perfume atomizers. As well, solvents are occasionally injected or mixed with alcoholic beverages.

EFFECTS OF SHORT-TERM USE[4]

CNS, behavioral, subjective: Experienced abusers may extol the virtues of certain solvents over others; however, there does not appear to be any objective evidence to support their claims. Such substances as carbon tetrachloride and benzene are clearly much more toxic than others.

Effects are rapidly perceptible after the initial inhalations. Inexperienced users often feel drowsy and may fall asleep. Other early effects include euphoria and dizziness as well as sensations of numbness, weightlessness, and dissociation from the environment; users claim that the euphoric effects of solvents tend to be similar to but far more pronounced that those of beverage alcohol. Shortly after the onset of early effects the following may also occur: giddiness, gregariousness, emotional disinhibition; motor incoordination and muscle weakness; slowed reflexes; slurred speech; impaired judgment; abnormal sensitivity to light; double vision; pupillary dilation; and ringing in the ears.

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[3] The principal advantage of a paper bag, rather than a plastic one, is that the probability of accidental suffocation is greatly reduced.

[4] The typical effects of these substances are generally dose-related, are similar to those of other sedative/hypnotic drugs, and at high doses are similar to those of anesthetics; however, there is a wide variation among users with regard to the type and intensity of effects experienced. Little is known about the combined effects of the variety of solvents found in commonly used products. What is presented here is a composite picture of the observations of clinicians and researchers.

Users may also experience a variety of perceptual distortions, which can include distortions of the shape, size, and color of objects and of time and space. Visual and auditory pseudohallucinations commonly occur (pseudohallucinations are known by the person to be unreal); however, true hallucinations also sometimes occur. There may be temporary delusions of omnipotence and invincibility, which may encourage reckless behavior. During this period of intense exhilaration, there may be bizarre behavior which can be harmful to the user and others. Impulsive violent behavior toward others occasionally occurs, and the user may purposely or accidentally injure himself. Occasionally users accidentally cause their own death by, for example, leaping from high places. Destruction of property is common.

While most users find the solvent-induced intoxication experience (the "jag") to be pleasurable, some become emotionally depressed; the depression can occasionally be so severe as to provoke suicide attempts. Some have suffered toxic psychosis manifested as delirium, disorientation, bizarre delusions, and hallucinations.

Cardiovascular: increased heart rate, irregular heartbeat, headache.

Respiratory: respiratory depression.

Gastrointestinal: nausea, vomiting, diarrhea.

Other: irritation and/or watering of the eyes, sneezing, coughing; nasal inflammation and nosebleed; chest pain, pains in the muscles and joints; and hangover after the effects of the solvents wear off.

The duration of the euphoric effects is typically between 15 and 45 minutes, provided that the user does not attempt to prolong the effects with additional administrations of solvents. The euphoria is followed by a period of drowsiness or stupor; there is a gradual decline in the intensity of the CNS-depressant effects, which generally disappear within one to two hours, although some side effects can last much longer. Partial or total amnesia may occur for the events of the solvent intoxication episode.

The sophisticated solvent abuser can maintain a level of desired intoxication for as long as 12 hours by taking spaced inhalations over this period. However, a prolonged period of concentrated and uninterrupted inhalation can result in a condition similar to severe alcohol or barbiturate intoxication; the user may even lapse into stupor or coma, which can be accompanied by depressed respiration, cardiovascular irregularities, and sometimes seizures. Significantly reduced oxygen intake may also occur with some methods of solvent inhalation; lack of sufficient oxygen to the brain can cause unconsciousness and brain damage with possibly fatal results.

EFFECTS OF LONG-TERM USE

There have been a number of unsubstantiated media reports linking severe brain damage to chronic solvent abuse; however, there is no conclusive evidence that regular abuse of any of these substances can cause significant and irreversible brain damage. Nonetheless, there is evidence that chronic exposure to or abuse of many solvents can be very harmful. The following identifies the toxic effects of some of the more common substances in chronically abused products.[5]

1. N-Hexane: Peripheral nerve damage, sometimes severe, has been reported to occur in some users after long-term abuse of this substance. Most gradually recover after discontinuing their abuse.
2. Toluene: A broad range of toxic effects implicating chronic abuse of toluene have been reported; however, none occur invariably. Damage to both central and peripheral nervous systems has been reported, as well as anemia and some damage to the liver and the kidneys. These effects appear to be reversible.
3. Trichloroethylene and trichloroethane: Severe and long-term liver and kidney toxicity has been reportedly caused by chronic

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[5] Similar effects, of course, are experienced by those who are accidentally exposed to high concentrations over extended periods of time in industrial settings.

abuse of both of these solvents; peripheral nerve damage has also been observed.

4. Acetone: Acetone has been demonstrated to cause significant damage to the mucous membranes of the respiratory tract.
5. Gasoline: Chronic inhalation of leaded gasoline can result in such serious complications as the accumulation of toxic levels of lead in the body.
6. Benzene:[6] Benzene is one of the most toxic solvents of abuse. Chronic abuse can cause bone marrow deterioration as well as severe damage to the heart, liver, and adrenal glands.

Other reported harmful effects which may occur in chronic solvent abusers include chronic (but reversible) cognitive impairment such as thinking and memory dysfunctions, reversible impairment of the liver, kidneys, lungs, and heart, and blood abnormalities. Chromosomal damage has been mentioned, but evidence is inconclusive.

More common and generally less serious effects include chronic tissue irritation throughout the respiratory system, tremors, sleep disorders, fatigue, loss of appetite, and persistent thirst.

Observations of psychological impairment among chronic solvent abusers suggest that most have significant personality problems. However, there is insufficient information at this time to conclude that there is a direct cause–effect relationship between the substance abuse and the psychological problems. Nonetheless, apathy, mood swings, depression, and paranoid thinking are common among solvent abusers.

LETHALITY

Inhaling or ingesting excessive amounts of any of the commonly abused solvents can cause significant CNS depression. Fortunately, fatalities directly arising from their toxic effects now occur only infrequently in abuse situations;[7] the user normally lapses into sleep or sometimes stupor before quantities sufficient to cause death are in-

[6] Benzene is now rarely available to Canadian abusers because of strict government controls over its commercial use.

[7] Such highly toxic solvents as carbon tetrachloride and benzene accounted for several deaths in the past.

haled. However, if the user is not awake and a receptacle such as a plastic bag remains firmly in place over the mouth and nose, there is a substantial risk of death from asphyxiation; in fact, this precise situation has caused a number of deaths. Some other accidental deaths have resulted from the bizarre or impaired behavior induced by solvent intoxication.

Several substances in this group have been associated with a phenomenon which is the most common cause of death among solvent abusers: sudden sniffing death (SSD). In these cases, death results from heart failure brought about by severely irregular heartbeat. In most instances the user had engaged in strenuous activity or was alarmed just prior to death. There in no conclusive evidence that such deaths are dose-related. (Sudden sniffing death is described in more detail below in connection with aerosols.)

Overdose of solvents, either accidental or intentional, has resulted in a number of deaths.[8] The ingestion of large quantities of solvents has sometimes been employed as a method of suicide. Careless storage of household solvents has too frequently resulted in small children being poisoned; many children have died after ingesting only a small quantity. In adults, a dose as small as 5–10 ml of trichloroethylene can be fatal.

TOLERANCE AND DEPENDENCE

Tolerance

The development of tolerance to the intoxicating effects of toluene, naphtha, and gasoline has been well demonstrated. For example, within a year's time, a glue sniffer may be using 8–10 tubes of toluene-containing plastic cement to achieve the desired intensity of effects that was initially produced by a single tube. With chronic and frequent abuse, tolerance is very likely to develop to other solvents.

Psychological and Physical Dependence/Withdrawal

Psychological dependence on solvents seems to be fairly common; many clinicians have observed that youthful solvent abusers are among the most intractable of their clients and that the recidivism rate is very

[8] Among the most highly toxic of these substances are carbon tetrachloride and benzene. The former has proven to be so dangerous that it can no longer be obtained in any product intended for commercial or household use in either Canada or the United States.

high. These users rarely seek professional assistance on their own; rather, almost all those in treatment have been compelled to undergo it by parents, legal authorities, or school authorities. With frequent abuse, the user acquires a craving for the psychological effects, and solvent use becomes an increasingly important part of everyday life. Generally, punishment and other types of controls tend to deter the abuse for only short periods of time.

Whether physical dependence results from chronic abuse of solvents is uncertain. Withdrawal symptoms have been reported to occur following abrupt termination of use; however, these phenomena are not universal, and there is no clear and documented syndrome among chronic users who abruptly abstain.[9] In some cases the following symptoms arise after abrupt termination of use: anxiety, depression, loss of appetite, irritability, hostile outbursts, dizziness, tremors, and nausea. Occasionally, toluene abusers have experienced severe symptoms similar to those occurring during alcoholic delirium tremens, although delusions (which accompany the alcoholic withdrawal syndrome) do not occur. Generally, when withdrawal symptoms do occur, they are mild (Cohen, 1977).

PATTERNS OF USE

Solvent inhaling is frequently undertaken in groups, with each person usually inhaling from his or her own bag or saturated cloth until the desired degree of intoxication is achieved. Repeated administrations may occur over a period of several hours in order to maintain this level of intoxication. Users typically discontinue administration either when their supply is exhausted or when they become too drowsy or fatigued to continue.

A 1981 survey of Ontario students in grades 7–13 appears to confirm the widely held notion that solvent inhaling ("glue sniffing") is inversely related to both the age and grade of students—that is, the lower the grade and the age, the greater the number of users: 3.7% of seventh graders acknowledge having used "glue" at least once during the past 12 months, while only 0.2% of thirteenth graders report use. With regard to other solvents, 5.5% of seventh graders and no thirteenth graders acknowledged use. This study also found that among solvent users boys and girls were roughly equally represented. However, other

[9] A consistent withdrawal syndrome does not even seem to occur among industrial workers who have been chronically exposed at excessively high levels.

studies have found the user ratio to be as high as 10 to one. Nonetheless, some recent studies suggest that solvent abuse among girls is increasing; furthermore, some of these studies have found higher rates of solvent abuse than those documented in the Ontario survey.

The large majority of young people who abuse solvents do so on an occasional or experimental basis. Those who more regularly abuse solvents are more likely to (1) come from economically disadvantaged homes; (2) perform less well in school; (3) have a substantially higher rate of truancy; (4) come from either unstable or broken homes, often with at least one alcoholic parent; and (5) have shown a poorer personal adjustment prior to the onset of their solvent abuse.

Many regular solvent abusers are subject to intense peer pressure to continue their abuse, and they are faced with the likelihood of ostracism should they make a serious attempt to quit—a prospect with which few of these troubled youths could adequately cope. Most youths outgrow solvent abuse, but there is a very high probability within this group of graduation to other drugs of abuse including heroin. Some others continue to abuse solvents into adulthood. What little valid research there is on solvent-abusing adults suggests that they tend to have significant adjustment problems; most also frequently abuse alcohol or other substances.

ABUSE POTENTIAL

Dependence Liability

When inhaled, solvents are rapidly absorbed into the bloodstream from the lungs, and the desired effects are then almost immediately perceptible. Most users claim to achieve a level of euphoria greater than that produced by alcohol. For these reasons, psychological dependence on this group of substances is common and the dependence liability of solvents is moderately high.

Inherent Harmfulness

Abuse of solvents can be harmful and even life-threatening; this knowledge is widespread among young people and probably deters a number of potential users. However, for some the risk of harmful consequences can actually foster the desire to use the drugs. Sometimes, troubled younger adolescents feel a strong need to increase their feelings of self-esteem and to achieve group acceptance by engaging in risk-taking behavior.

Availability

There are few drugs of abuse as cheap and as easily available to young adolescents as solvents; low cost of and ease of access to most desired solvents contribute to their high potential for abuse.

AEROSOLS:

DRUG SOURCE

Certain halogenated hydrocarbons, principally the fluorinated hydrocarbons (also called freons or fluorocarbons) and to a lesser extent trichloroethane, were formerly subject to widespread abuse as inhalants in those products in which they functioned as aerosol propellants. All of these substances are produced through chemical synthesis by the chemical industry.

TRADE NAMES

None of these substances has any medical use.

Fluorinated hydrocarbons usually bear numerical designations for simplicity of reference; hence, trichlorofluoromethane is referred to as Propellant 11, and one manufacturer's trade name for this substance was Freon 11. Another important freon is Propellant 12.

STREET NAME

Gas.

COMBINATION PRODUCTS

Aerosol containers have one or more propellants in the form of pressurized liquids or gases which escape when the valve is released. The solid or liquid contents propelled by the gas vary from foodstuffs through antiseptics and cookware coating agents to paints.

In some instances, other types of hydrocarbons, such as isobutane, were used as propellants in combination with freons; this combination was widely used in such products as cosmetics and household cleaners.

[10] Trichloroethane was also used in the past as a low-pressure propellant in medicated vapor aerosols.

The contents of the can sometimes also included other solvents liable to abuse, such as trichloroethane in cleaning fluids,[10] toluene in glues and paint removers, and alcohol in hair sprays.

MEDICAL USES

None. However, aerosol-type packaging is used for a variety of products intended for medical use, including antibacterial, antifungal, and local-anesthetic solutions and powders intended for application to skin or mucous membranes.

PHYSICAL APPEARANCE

The propellants in spray cans are volatile liquids or compressed gases. Propellants 11 and 12, the most toxic of the freon propellants, are colorless, noncorrosive, nonflammable gases at room temperature. They have a faint ether-like odor. Both of these substances have refrigerant properties.

DOSAGE

Since the composition and purposes of this class of products vary so widely, generalized statements regarding typical abusive doses are not possible.

ROUTES OF ADMINISTRATION

Freons and other propellants may be separated from the other contents of a pressurized container by a variety of methods (Hofmann, 1975).

1. The container may be held and the valve pressed in such a way as to permit only the gas to be released for direct inhalation.
2. The contents may be filtered through a rag or cloth held firmly over the mouth and nose so that mainly the gas is inhaled.
3. The propellants and other contents of the container may be sprayed into a plastic or paper bag, or sometimes into a balloon, and then inhaled directly (a method common among "glue sniffers").
4. Some abusers spray the propellants and other contents directly into the mouth.

EFFECTS OF SHORT-TERM USE[11]

These substances can produce a state of pleasurable intoxication which can include sensations of weightlessness and numbness; emotional disinhibition; motor incoordination; impaired judgment; perceptual distortions; pseudohallucinations and sometimes true hallucinations; and delusions of grandeur. Bizarre behavior induced by these drugs can sometimes result in harm to the abuser and others and in the destruction of property.

Heartbeat can be abnormally rapid and irregular, blood pressure can quickly drop, respiration may be depressed, and temporary spasms in the bronchial tubes occasionally occur. Irritation of the eyes, throat, and nasal passages is frequent, as is minor gastrointestinal upset.

Concentrated, uninterrupted inhalation of freons can result in a condition similar to severe alcohol intoxication, which may be accompanied by coma and potentially dangerous cardiac irregularities. Seizures have occasionally occurred.

EFFECTS OF LONG-TERM USE

Kidney and liver damage may result from chronic abuse of (or accidental exposure to) freons. Reversible damage to respiratory-tract tissue and mucosal membranes can also occur. Sores on the nose and mouth ("glue sniffer's rash") are common. Freon abusers may also suffer the following: chronic fatigue; nosebleeds; pallor; memory impairment; diminished ability to think clearly or logically; tremors; unsteady gait; constant thirst; loss of appetite accompanied by weight loss; and apathy, mood swings, emotional depression, and paranoid thinking.

LETHALITY

There is substantial evidence that among solvents of abuse, freons are the most likely agents to cause sudden sniffing death (SSD), and that they account for more than half of all such deaths.[12] The pattern

[11] Most effects produced by freons are similar to those arising from abuse of other solvents and, therefore, will be only briefly summarized here. However, freons generally have a greater toxic effect on the heart.

[12] A number of sudden sniffing deaths have also been caused by trichloroethane.

resulting in sudden sniffing death is well established, although it is uncertain why some users are more vulnerable than others. After several consecutive and deep inhalations, the user immediately engages in strenuous activity (e.g., running or wrestling) or is subjected to unexpected stress (e.g., being discovered), and often appears to have been startled or is panicky. Within a few seconds after the onset of the stress or vigorous activity, collapse and death rapidly ensue. The cause of death is generally considered to be sudden heart failure resulting from severe cardiac arrhythmia, but the specific mechanisms causing the phenomenon are not yet understood. Several hundred sudden sniffing deaths have been recorded in North America, Europe, and Japan during the past two decades.

Deaths involving freon propellants have also been attributed to other causes. These substances can produce laryngospasm or "airway freezing"—the latter caused by the rapid vaporization of freons in the throat. Either effect can result in total occlusion of the respiratory passage and death from suffocation. Death from suffocation can also occur if the user loses consciousness while a plastic bag containing the inhalant remains in place over the nose and mouth. Some substances propelled by the aerosol, such as paints, can themselves produce serious toxic effects. Finally, some deaths arise from the dangerous and bizarre behavior induced by inhalant intoxication.

TOLERANCE AND DEPENDENCE

With regular use, tolerance develops to the desired psychoactive effects of freons; psychological dependence can be as severe as that resulting from abuse of other solvents. However, with regard to physical dependence, there is no firm evidence of a distinct withdrawal syndrome resulting from abrupt termination of regular freon abuse.

PATTERNS OF USE

Abuse of freons was widespread until a few years ago. Nowadays, the freons in aerosols have been almost totally replaced in Canada and many other countries by other less toxic propellants. The toxicity of freons was one important factor in the discontinuation of their commercial use. However, another key concern was the fear expressed by many scientists that freons could break down the ozone layer, the atmospheric layer surrounding Earth which shields the planet from the harmful effects of ultraviolet rays on climate and health.

ABUSE POTENTIAL

The dependence liability of freons is similar to that of other solvents of abuse, although freons are generally more toxic. However, their abuse potential is now virtually nonexistent because they are no longer generally available.

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A CLASSIFICATION OF ABUSED SOLVENTS

1. *Aliphatic and Aromatic Hydrocarbons:*
   Hexane
   Naphtha
   Petroleum distillates
   Gasoline
   Benzene
   Xylene
   Toluene

2. *Halogenated Hydrocarbons:*
   Trichloroethylene
   1,1,1,trichloroethane(methylchloroform)
   Carbon tetrachloride
   Ethylene dichloride
   Methylene chloride
   Chloroform
   Halothane

   Freons:
   Trichlorofluoromethane(FC11)
   Dichlorodifluoromethane(FC114)
   Cryoflurane
   Dichlorotetrafluoromethane(FC12)

3. *Aliphatic Nitrites:*
   Amyl nitrite
   Isobutyl nitrite

4. *Ketones:*
   Acetone
   Cyclohexanone
   Methyl ethyl ketone
   Methyl isobutyl ketone
   Methyl butyl ketone
   Methyl amyl ketone

5. *Esters:*
   Ethyl acetate
   Amyl acetate
   Butyl acetate

6. *Alcohols:*
   Methyl alcohol
   Isopropyl alcohol

7. *Glycols:*
   Methyl cellulose acetate
   Ethylene glycol

8. *Ethers*

9. *Gases:*
   Nitrous oxide

Source: S. Cohen, Inhalant abuse: an overview of the problem, p. 5, in *Review of Inhalants: Euphoria to Dysfunction*, C.W. Sharp and M.L. Brehm (Eds.), NIDA Research Monograph 15, National Institute on Drug Abuse, Rockville, Md., 1977.

Isopropyl Alcohol

(Isopropanol)

DRUG CLASS: TOPICAL ANTISEPTIC AND
RUBEFACIENT;
POISON

SYNOPSIS

Isopropyl alcohol is a synthetic chemical product widely used in rubbing alcohol compounds and certain cosmetics such as hand lotions and aftershave lotions. When ingested it possesses mild inebriant properties. Poisoning by isopropyl alcohol occurs as a result of the drug's conversion to acetone, for the accumulation of acetone in the body can cause kidney impairment, coma, and frequently death from respiratory arrest. The lethal dose of isopropyl alcohol has been estimated at approximately 12–24 cl (4–8 oz). Some skid-row alcoholics not only purposely ingest isopropyl alcohol but actually express a preference for it over ethyl (beverage) alcohol, in spite of their awareness of its hazards. However, in most cases skid-row alcoholics consume it out of desperation or without knowledge of its lethal potential.

DRUG SOURCE

Isopropyl alcohol is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Isopropyl alcohol is generally a component in combination products (see below).

STREET NAMES

None in common use.

COMBINATION PRODUCTS

Isopropyl rubbing alcohol is diluted with water and rubbing compounds to a concentration of approximately 70%; sometimes colors and perfumes are added. It is also a component of hand lotions, aftershave lotions, and similar cosmetics, antifreeze solutions, and quick-drying inks.

Skid-row alcoholics sometimes combine isopropyl alcohol with ethyl alcohol.

PHYSICAL APPEARANCE

In pure form, isopropyl alcohol is a clear, colorless, volatile liquid.

DOSAGE

Medical

In products for application to unbroken skin for its antiseptic and cooling effects, the concentration of isopropyl alcohol is 70% or greater.

Nonmedical

Isopropyl alcohol has been purposely ingested by some advanced alcoholics in the form of rubbing alcohol or other products. Skid-row alcoholics have been known to combine it with ethyl alcohol.

While single doses of 12–24 cl (4–8 oz) are normally fatal, there is at least one documented case report of a chronic alcoholic surviving after ingesting 42 cl (i.e., a pint) of 70% pure isopropyl alcohol.

ROUTES OF ADMINISTRATION

When isopropyl alcohol is ingested orally, it is usually taken by those ignorant of its toxicity.

Inhalation of its vapors in a poorly ventilated area can produce toxic effects.

EFFECTS OF SHORT-TERM USE: LOW DOSES[1]

CNS, behavioral, subjective:[2] mild inebriation, dizziness, mild motor incoordination, and other relatively mild nervous and muscular disturbances.

Cardiovascular: mild to moderate drop in blood pressure; protracted headache.

Gastrointestinal: diarrhea, painful gastritis, nausea and vomiting.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

Intensification of low-dose effects may occur as well as any of the following effects:

CNS, behavioral, subjective: confusion, possibly marked motor incoordination, stupor, and coma.[4] The clinical picture may be complicated by the presence of other ingredients in isopropyl alcohol products, particularly volatile aromatics (e.g., camphor, naphthalene); such combinations can result in a syndrome of CNS stimulation with motor restlessness, extreme apprehension, hallucinations, and disorientation.

Cardiovascular: marked drop in blood pressure, slow pulse, sometimes circulatory collapse and shock, low body temperature.

Respiratory: respiratory depression.

Gastrointestinal: gastrointestinal pain and hemorrhage, nausea and vomiting, diarrhea.

Other: possibly severe kidney impairment.

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[1] Approximately 3 cl (1 oz) or less taken orally by nontolerant users.

[2] Effects are generally experienced for a longer period than with comparable amounts of ethyl alcohol because isopropyl alcohol is metabolized more slowly.

[3] Approximately 6 cl (2 oz) or more taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

[4] Protracted inhalation of concentrated vapors of isopropyl alcohol in poorly ventilated areas can produce deep coma.

EFFECTS OF LONG-TERM USE

Even among skid-row users, isopropyl alcohol is rarely used on a regular basis to the exclusion of ethyl (beverage) alcohol; for this reason, chronic effects directly attributable to isopropyl alcohol are not fully known. However, severe kidney and liver impairment are likely.

LETHALITY

The lethal potential of isopropyl alcohol is much higher than that of ethyl alcohol and somewhat lower than that of methyl alcohol. Doses of 12–24 cl (i.e., approximately 4–8 oz) of isopropyl alcohol can kill an adult, and much lower doses can kill a small child. In cases of lethal overdose, death is generally preceded by extremely low blood pressure, deep coma, and respiratory arrest.

Because even small doses of this substance can be fatal for small children, care must be taken to store it out of their reach.

Isopropyl alcohol has been implicated in both successful and unsuccessful suicide attempts.

TOLERANCE AND DEPENDENCE

Researchers have reported that among those few skid-row alcoholics who regularly drink isopropyl alcohol, tolerance to its inebriating effects does appear to occur.

PATTERNS OF USE

A small number of derelict alcoholics actually express a preference for isopropyl alcohol and other toxic alcohols over ethyl alcohol. Research interviews clearly indicate that all of these regular users are aware of the toxic effects of the nonbeverage alcohols. Furthermore, skid-row workers report that many of those dependent on ethyl alcohol also occasionally resort to isopropyl alcohol. They are most likely to do so out of desperation when they are on the threshold of withdrawal sickness and cannot buy ethyl alcohol or otherwise obtain it.

ABUSE POTENTIAL

Because of the toxicity of isopropyl alcohol, it is very rarely abused outside of the skid-row community.

LSD

(Lysergic Acid Diethylamide)

DRUG CLASS: HALLUCINOGEN

SYNOPSIS

LSD (lysergic acid diethylamide) is the most powerful of the known hallucinogens. In such minute doses as 50–100 micrograms (0.05–0.1 mg) it can produce significant changes in perception, mood, and thought. These changes include visual hallucinations and distortions which the user usually knows to be unreal. Synesthesia—the paradoxical perception of the senses melding together—can be experienced such that, for example, users may believe they are "seeing" music or "hearing" visual patterns. Normal boundaries of identification between the self and the environment frequently disappear under the influence of LSD, and there may be distortions of body image, space, and time (minutes may seem to pass as slowly as hours).

The above experiences are often accompanied by periods of deep introspection, in which the users may feel they are gaining great insights or may feel alienated from themselves and their environment. Any given LSD "trip" may produce in the user a sense of wonder and joy or a sense of anxiety, fearfulness, or even panic. Even those users who have experienced the drug positively on some occasions are not immune from having an adverse episode ("bad trip") on other occasions.

LSD can precipitate severe psychotic episodes in a small minority of users who have not manifested these symptoms previously; the symptoms may persist long after the drug has been eliminated from the body. A psychotic episode may be characterized by bizarre behavior, delusional thinking, terror, and true hallucinations (i.e., hallucinations which the user believes to be real).

LSD, like certain other hallucinogens, cannot be taken continuously for more than a few days and still retain its psychic potency. Tolerance develops quickly, and the user must abstain for at least a few days in order to regain sensitivity to the desired effects. Physical dependence is not known to occur.

DRUG SOURCE

LSD is produced through chemical synthesis in illicit laboratories, except for a small amount which is legally produced exclusively for research purposes.

TRADE NAMES

Not applicable; not used medically except for research.

STREET NAMES

Acid, barrels, blotters, California sunshine, cube, domes, flats, frogs, lids, wedges, windowpane.

DRUG COMBINATIONS

Unknown to the purchaser, LSD combinations encountered on the street most often contain PCP (phencyclidine).[1]

Some preparations in earlier years included amphetamines. LSD has been occasionally added to alcoholic beverages. A combination of LSD with strychnine and methamphetamine, "Blue Cheer" (alleged to be widespread in earlier years), has rarely been found in Canadian street-drug analysis programs.

MEDICAL USES

There is currently no accepted medical use for LSD.

PHYSICAL APPEARANCE

When pure, LSD tartrate is a white odorless crystalline material which is soluble in water. However, LSD is so potent that an effective dose of pure drug is so small as to be virtually invisible; therefore, it is diluted with other materials before distribution in the form of capsules, tablets, solution, gelatin sheets, pieces of blotting paper, etc.

[1] Street-drug preparations alleged to contain LSD often contain additional drugs or are in fact other drugs. The reverse is also true; street drugs alleged to contain a different substance sometimes contain LSD.

DOSAGE

Medical

LSD has been used medically almost exclusively as an investigational drug, especially in psychotherapy and in the treatment of alcoholism. In these uses 100 micrograms (0.1 mg) would be considered an average dose.

Nonmedical

Street-drug preparations usually range from 40 to 500 micrograms (0.04–0.5 mg). Approximately 40 micrograms will produce mild effects.

ROUTES OF ADMINISTRATION

LSD may be taken orally, inhaled, or injected.

EFFECTS OF SHORT-TERM USE[2]

CNS, behavioral, subjective: There is a fairly wide variation among users in the possible perceptual, cognitive, and emotional experiences produced by LSD. In addition to the size of the dose, drug effects are also influenced by the setting, the user's expectations, past drug experiences, and personality. It is not unusual for a user to experience differing reactions to LSD during different drug-taking episodes. Early effects[3] can include numbness, muscle weakness, muscle twitching, rapid reflexes, tremulousness, impairment of motor skills and coordination, and pupillary dilation. Often there is early anxiety or sometimes exhilaration; the latter is likely due to the user's expectations, as it may occur prior to the onset of hallucinogenic actions. Seizures also infrequently occur. Later effects can include the following:

1. There may be vivid perceptual distortions, usually

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[2] 100 micrograms taken orally by nontolerant users. Increasing doses of LSD tend to produce quantitative changes (i.e., greater intensity) rather than qualitative changes (i.e., different symptoms). It has been demonstrated that "Between the dose ranges of 1–16 micrograms per kg, the severity of psychophysiological effects of LSD is proportional to the dose" (Jaffe, 1975, p. 310). For instance, this dose range for a 73 kg (160 lb) person would be between approximately 70 and 1,100 micrograms.

[3] I.e., occurring within 15–45 minutes after administration.

visual, such as "pseudohallucinations" and "pseudoillusions" (i.e., the user is aware that the experience is not real).

2. Time may be distorted (minutes may seem to pass as slowly as hours).
3. There may be distortions of space, which can prove hazardous if the user is driving or in some other potentially dangerous situation, such as standing near the edge of a high balcony.
4. There may be distortions of body image. Some users feel heavy and "pulled down" by gravity, while others experience sensations of weightlessness and floating.
5. Perception of recognized boundaries between self and environment is diminished and may be completely lost. For some users this generates a feeling of oneness with the universe, but for others it can be terrifying, as anchors in both internal and external reality may appear to be no longer present.
6. Control over thinking processes and concentration can be markedly diminished.
7. Synesthesias frequently occur: that is, one sensory modality is melded with another, as with music being "seen" or color being "heard."
8. Recent or even long-forgotten memories can vividly resurface and possibly blend with current experience.
9. Otherwise insignificant thoughts may take on deep meaning.
10. Parts of the user's body or trivial objects may be the subject of careful and prolonged scrutiny and may also take on magnified importance or meaning.
11. In fact, all sensory experiences tend to be heightened; the user perceives brighter colors, sharper definition of objects, increased hearing acuity, more sharply distinguished taste, etc.
12. Different emotions may appear to exist simultaneously or rapidly follow each other.
13. Some users withdraw and appear to be indifferent to

their surroundings; others may become hypervigilant; and many alternate between these states.

14. Users may feel that they are undergoing a profound mystical, religious, or "cosmic" experience—for many users perhaps the most desired effect.

ADVERSE REACTIONS

Many users have experienced unpleasant reactions to the effects of LSD. Fearfulness, anxiety, and depression may occur even in experienced users who have had no prior adverse reactions. Some users undergo highly adverse reactions to the above effects (i.e., "bad trips"). Users can feel that they are losing their identity; they may fear that they are disintegrating into nothingness and that there is no reality. "Pseudohallucinations" may give way to terrifying true hallucinations. Acute paranoid states may occur, and bizarre delusions may be manifested in such extreme behavior as violent, homicidal, or suicidal actions. Severe confusion and disorientation may also provoke highly inappropriate behavior. Nonetheless, in spite of their severity, these symptoms usually rapidly decline in intensity and disappear after the drug is metabolized and excreted from the body.[4]

Because adverse effects are particularly common among new users, early LSD "trips" are usually taken in the company of experienced users who are familiar with the effects of the drug and therefore can often forestall acute panic reactions.

Cardiovascular: increased blood pressure and heart rate; elevation of body temperature and sweating, which may alternate with chills and shivering (all are early effects).

Respiratory: abnormally rapid and deep breathing (an early effect).

Gastrointestinal: nausea and vomiting; suppression of appetite (all are early effects).

The effects of a single dose of LSD, when taken orally, are usually experienced within less than a half-hour, peaking in three to five hours; the gradual cessation of effects is usually complete within 12 hours.

CLINICAL USE OF LSD

Some medical researchers began early investigations with LSD in the hope that it would ameliorate psychological disturbance in their patients by inducing greater insight and acceptance of self. It was reasoned that the LSD experience should help patients to temporarily detach their conscious mind from reality; under this condition they might be more able to deal with repressed painful experiences and also to modify their perception of self and external reality. Therefore, LSD was used experimentally with a spectrum of emotional conditions, ranging from alcoholism to fear of death in terminally ill patients. Unfortunately, such treatment experiences were not demonstrated to have lasting impact. Clinical use of LSD is now rare; however, some researchers and physicians continue to claim that not enough experimentation was undertaken and that the negative conclusions regarding the potential of LSD therapy were premature.

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[4] In some cases this psychotic state may last for several days or longer.

EFFECTS OF LONG-TERM USE

Flashbacks

Perhaps the persistent phenomenon most frequently associated with LSD use is "flashbacks"—spontaneous recurrences of specific experiences which originally occurred during an LSD episode. Typically they are brief, lasting only a few minutes or less. Their recurrence is not predictable, nor are they experienced by the majority of LSD users. They may occur shortly after an LSD episode or, in some cases, over a year later. They may be elicited by the use of other psychoactive drugs, such as cannabis. Some users acknowledge having experienced only one flashback, and others report several. Some report the experience to be pleasant, while others feel acute panic. Regular users are more likely to experience flashbacks than those who have taken a single LSD "trip."

Visual images are the most frequently reported form of flashback, ranging from formless colors to very frightening hallucinations. Less frequently, flashbacks involve other sensory modalities—taste, smell, hearing, body sensations, touch, and balance. They may also recur in the form of distortions of time, space, body image, or reality. Their etiology is unknown.

Amotivational Syndrome

An amotivational syndrome has been observed in some users of LSD as well as of marijuana. The common manifestations of this syndrome are increasing apathy and decreasing interest in both one's environment and social contacts, loss of effectiveness, passivity, diminished frustration tolerance, and lack of interest in planning ahead. As well there is often a disregard for typical social conventions such as appropriateness of dress and public comportment. While it may be tempting to suggest that these behaviors result exclusively from chronic LSD use, a causal relationship of this nature is extremely difficult to demonstrate because of the numerous factors involved. It has been proposed that this syndrome may, in many instances, have been more realistically attributed to certain aspects of a lifestyle adopted by many young people during the 1960s and early 1970s, rather than solely to drug use. Conservatively, it may be suggested that in some respects, the use of LSD and other drugs may serve to foster amotivational syndrome in some users, and amotivational syndrome as a lifestyle may serve to foster the use of LSD and other drugs in others.

LSD-Precipitated Psychosis

Acute psychotic episodes caused by a single dose of LSD ordinarily last for several hours. However, both a single dose and chronic use have resulted in a protracted period of psychosis for some individuals; this psychosis in many respects resembles paranoid schizophrenia and is characterized by true hallucinations (mainly visual[5]), delusional thinking, and bizarre behavior. Although many of these individuals are believed to have been latent psychotics prior to their use of LSD, some had previously exhibited little or no obvious personality disturbance.

Other Effects

There is inconclusive evidence in humans of chromosomal damage resulting from chronic LSD use, and the significance of such damage (when found to occur) is also unclear. There appears to be a higher risk of spontaneous abortion and congenital abnormalities in offspring of women who have regularly used LSD during pregnancy; however, in almost all instances studied, the mothers had also used other drugs during their pregnancy, and therefore the causal relationships are difficult to determine. Although there has also been concern about the possibility of brain damage in chronic users, again causality has not been established.

LETHALITY

No deaths resulting exclusively from acute LSD overdose have been reported. However, cases of suicide during or following LSD intoxication have occurred. Other results of violent or hazardous behavior have included accidental (sometimes bizarre) fatalities, homicides, and self-mutilations.

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[5] However, paranoid schizophrenics more often experience auditory hallucinations.

TOLERANCE AND DEPENDENCE

Tolerance develops particularly rapidly to the subjective effects of LSD,[6] and as well to its effect on blood pressure, pupils, and reflexes. With consecutive daily doses, often by the third or fourth day no amount of the drug is able to produce the desired effects. After three to four days' abstinence, normal sensitivity returns. Once tolerance to LSD develops, the effects of several other hallucinogens—psilocybin, mescaline, and other lysergic derivatives—also cannot be experienced until after the minimum period of abstinence from LSD. This phenomenon is referred to as cross-tolerance.

Chronic use of LSD does not appear to result in the development of physical dependence; that is, no withdrawal sickness after its discontinuance has been reported.

The degree to which psychological dependence on LSD develops varies considerably among users. For some regular users, LSD plays the central role in their lives and they experience a compulsive need to continue using the drug. For them, temporary unavailability of LSD can result in anxiety or even feelings of panic. Rarely will they voluntarily discontinue their drug use. They represent a small minority of LSD users, and in the street vernacular are derogatorily referred to as "acid heads" or "acid freaks."

PATTERNS OF USE

LSD is not a drug subject to everyday use. Since tolerance to the subjective effects develops rapidly, continued daily use is pointless. Many regular LSD users are "weekend trippers"—restricting their use to no more than a few days each week; for many, even less frequent use is reported. However, surveys indicate that LSD is not the exclusive drug of use among this population, who often take such drugs as cannabis and sedative/hypnotics during periods of LSD abstinence. As well, many users of other drugs have experimented with LSD once or twice, primarily for the experience and without any real interest in continuing to use it.

Although use of LSD declined sharply in the mid-1970s, recent surveys of Ontario high school students suggest it is once again increasing.

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[6] See Tolerance—Tachyphylaxis under Drug Tolerance: The Body's Adaption to Drugs in section 1.

ABUSE POTENTIAL

Dependence Liability

Physical dependence on LSD does not occur, and only a small fraction of users become psychologically dependent on it.

Inherent Harmfulness

LSD can cause severe psychic distress (the "bad trip") in some users, and such occurrences cannot be predicted. The "flashback" experience, which can unexpectedly come upon the user at any later point, can also be quite distressing. Many potential users have probably been deterred by hearing about these negative effects from their own contacts and by the adverse publicity which LSD has received for a variety of reasons, some without scientific justification.

Availability

The availability of LSD tends to vary with its popularity on the street. When the drug is in fashion it is usually quite easy to obtain; at other times it can be very difficult to find. Other substances, such as PCP, are frequently passed off as LSD to the unsuspecting buyer.

REFERENCE

Jaffe, H.J., Drug addiction and drug abuse, in *The Pharmacological Basis of Therapeutics*, L.S. Goodman and A. Gilman (Eds.), Macmillan, New York, 1975.

MDA

(Methylenedioxyamphetamine)

DRUG CLASS: HALLUCINOGEN WITH STIMULANT PROPERTIES

SYNOPSIS

MDA (methylenedioxyamphetamine) is a hallucinogenic drug with properties similar to both LSD and the amphetamines. Because it is alleged to produce emotional closeness to others, serenity, and relaxation, street users have termed it the "love drug." There is no medical use for MDA, although it was investigated for use in facilitating psychotherapy.

DRUG SOURCE

Produced through chemical synthesis, almost exclusively in illicit laboratories.

TRADE NAMES

Not applicable.

STREET NAME

Love drug.

COMBINATION PRODUCTS

None known.

MEDICAL USES

There is no medical use for MDA.

PHYSICAL APPEARANCE

MDA hydrochloride in its pure form is a white powder, but on the street it ranges from white through yellow to brown depending on its state of purity. Occasionally it appears in the form of an amber liquid.

DOSAGE

Medical

Not applicable. However, before MDA achieved notoriety in the drug culture, it was investigated for use in facilitating psychotherapy. The dose range was from 40 to 150 mg.

Nonmedical

From approximately 120 mg upwards.

ROUTES OF ADMINISTRATION

MDA is usually taken orally, although it is sometimes sniffed or injected.

EFFECTS OF SHORT-TERM USE: LOW TO MODERATE DOSES[1]

Increasing the dose in the low to moderate range generally results in correspondingly greater intensity of the subjective and somatic effects; however, there are individual differences in sensitivity to the drug. The following effects may occur:

CNS, behavioral, subjective: The subjective experiences vary among individual users, and many intangible factors, such as mental attitude and expectations, may affect the experience. Hallucinations, perceptual distortions, and closed-eye imagery rarely occur with MDA, unlike with LSD, mescaline, or psilocybin. Feelings of peacefulness, tranquility, and emotional closeness to others are frequently reported (hence its nickname "love drug"). Aesthetic enjoyment, intuitive insight, and a heightened state of consciousness, reported by experienced users to be similar to the effects produced by LSD, are also likely to occur at relatively low doses.

At moderate doses, the effects tend to approximate even more closely those of LSD, but without the hallucinations and perceptual distortions. Intensification of feelings, heightened but not distorted sensory awareness, spontaneous recalling of events long past, and a belief of greater awareness and self-insight are among the more commonly reported effects.

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[1] Single doses between 60 and 150 mg.

Although the MDA experience appears to be rewarding for most users, mild to moderate adverse effects have occurred for some. These include confusion, fatigue, amnesia for the experience, and anxiety occasionally lasting for up to two days after the episode. In some users, overactivity and overstimulation resembling that produced by amphetamines have also occurred during the latter stages of the episode. More severe adverse effects can occur when MDA is taken in combination with other hallucinogenic or stimulant drugs.

Additional effects include decreased appetite, pupillary dilation, periodic tensing of the neck and jaw muscles, and at moderate doses grinding of the teeth.

Cardiovascular: increased blood pressure and pulse rate, increased body temperature, and perspiration.

Gastrointestinal: dryness of mouth, throat, and nose.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[2]

At high doses, many symptoms produced by MDA are similar to those at high doses of the major amphetamines.

Certain hallucinogens, such as LSD, mescaline, and psilocybin, are relatively benign at higher doses. By contrast, high single doses of MDA have been observed to produce undesirable and/or very harmful effects in some users. Among these are:

CNS, behavioral, subjective: fixed and widely dilated pupils; hyperactive deep-tendon reflexes; extreme reflex hyperexcitability to auditory, visual, and tactile stimuli; agitation; hallucinations; delirium; convulsions; and coma.

Cardiovascular: very high body temperature and profuse sweating.

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[2] Doses of 300–500 mg have produced these effects in some users.

Respiratory: respiratory insufficiency produced by chest-muscle spasm.

Other: erection of body hair.

The range of time for initial effects tends to be between 30 and 60 minutes; the effects peak at approximately 90 minutes and persist up to 8–12 hours.

EFFECTS OF LONG-TERM USE

Not known. A particular problem in gathering accurate information about the specific effects of chronic MDA abuse is that many people who use MDA are also likely to use other drugs concurrently.

LETHALITY

A relatively small number of MDA-associated deaths resulting from respiratory insufficiency were reported in the early 1970s (five in Ontario in a 13-month period), but it is likely that there are others that have remained undocumented. It is important to note that more dangerous drugs such as PMA (paramethoxyamphetamine) and PCP (phencyclidine) have been sold on the street as MDA.

TOLERANCE AND DEPENDENCE

Tolerance and/or dependence have not been reported. There have been no extensive clinical investigations of the effects of MDA on humans.

PATTERNS OF USE

Recent surveys and analyses of street drugs suggest that MDA use has declined and is now infrequently encountered in Canada. PCP is sometimes misrepresented to be MDA.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of MDA is not known, but it is likely that it is very low.

Inherent Harmfulness

In the low to moderate dose range—which, in the case of MDA, includes doses sufficient to produce the desired effects—adverse effects tend to be relatively mild. Doses high enough to produce hazardous effects are not likely to be intentionally self-administered.

Availability

Given the usually pleasant effects associated with low to moderate doses of MDA (the "love drug"), it is difficult to explain its almost complete disappearance in Canada. One explanation concerns the waxing and waning in popularity of drugs of abuse. For example, the use of LSD among young people rapidly declined from a peak in the late 1960s until the late 1970s, after which it began to return to popularity.

Meperidine

DRUG CLASS: NARCOTIC ANALGESIC;
OPIOID

SYNOPSIS

Meperidine is a synthetic narcotic analgesic; its principal clinical use is for relief of moderately severe to severe pain. The analgesic potency of meperidine when administered by injection is substantially less than that of morphine. However, in contrast to many other narcotic analgesics (including morphine), meperidine retains much of its potency when administered orally. Furthermore, tolerance to its analgesic effects develops gradually, and therefore a patient can be maintained on the same daily dose for several weeks or even months.

Both physical and psychological dependence can develop with long-term use, even at low daily doses. When meperidine is chronically administered by injection, significant local irritation of tissue occurs and continued needle use becomes increasingly painful. The principal toxic effects of meperidine when administered in high doses are respiratory depression and central nervous system excitation; the latter is manifested in twitches, tremors, and agitation—and, in very high doses, in convulsions and toxic psychosis. For these reasons, and because the degree of euphoria produced by meperidine is less intense than that of heroin or morphine, meperidine is usually not the drug of choice among street users. However, because of its availability in their work place and because of its lower dependence liability (when compared, e.g., with morphine) meperidine is the most commonly reported drug of abuse among physicians and nurses who are dependent on narcotic analgesics.

DRUG SOURCE

Meperidine is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Demer-Idine, Demerol.

STREET NAMES

None in common use.

MEDICAL USES

- primarily for relief from moderate to severe pain, including pain associated with childbirth;
- occasionally for preoperative analgesia and sedation.

PHYSICAL APPEARANCE

Meperidine appears as tiny white crystals, very soluble in water and soluble in alcohol, and slightly bitter to the taste.

DOSAGE[1]

Medical

- for moderate pain—50–100 mg orally, or by subcutaneous or intramuscular injection, up to every three hours;
- for severe pain—up to 150 mg by subcutaneous or intramuscular (or occasionally intravenous) injection, up to every three hours.

Nonmedical

Typical single doses for a chronic abuser may exceed 200–300 mg, and administration of each dose may be as frequently as every three hours or less. Amounts of up to 3 to 4 grams per day have been reported.

ROUTES OF ADMINISTRATION

Orally by tablet, or by subcutaneous, intramuscular, or intravenous injection (the last route being preferred by many abusers).

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[1] When injected subcutaneously, 80–100 mg meperidine equals 10 mg morphine in analgesic potency.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, behavioral, subjective: suppression of the sensation of and emotional response to pain; euphoria; mild clouding of mental function, drowsiness, lightheadedness, dizziness; in some cases mild depression and anxiety; visual disturbances.

Cardiovascular: slightly rapid heart rate or in some cases slightly slowed heart rate; sweating; occasionally headache.

Respiratory: slight reduction in respiratory rate.

Gastrointestinal: dry mouth; nausea, vomiting; constipation; loss of appetite.

Other: itchy or prickly skin; urinary retention; reduced libido.

The effects of meperidine last for a shorter period of time than for most narcotic analgesics, usually about three hours.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

Intensification of low-dose effects may occur. As the dose increases:

1. Sensitivity to painful stimuli decreases.
2. There is a greater probability of sleep.
3. Ability to concentrate is increasingly impaired.
4. Breathing becomes progressively slower and more shallow.
5. Heart rate gradually slows and blood pressure decreases.
6. In contrast to many other narcotic analgesics, higher doses of meperidine can produce pupillary dilation.
7. Also in contrast to many other narcotic analgesics, higher doses of meperidine can occasionally produce CNS excitation manifested in muscle twitches and tremors.

[2] Single doses within the therapeutic range, oral or by injection, in nontolerant users.

[3] Single doses above the therapeutic range in nontolerant users, or lower doses in particularly sensitive individuals.

At very high doses (i.e., overdose) meperidine can produce disorientation, hallucinations, grand mal seizures, deep sleep possibly progressing to stupor or coma, shallow and markedly slowed breathing, slow heart rate, low blood pressure, cyanosis, low body temperature, flaccidity of skeletal muscles, and cold and clammy skin.

EFFECTS OF LONG-TERM USE

Chronic subcutaneous injection of meperidine is both considerably more painful and more irritating than for most other common narcotic analgesics. Round scars on the skin and numerous hardened areas beneath the skin are commonly observed on the arms of abusers of injectable meperidine. In spite of the discomfort associated with chronic needle use, they must administer the drug more often than do heroin- or morphine-dependent users, as the duration of action of meperidine is considerably shorter. Mild and early withdrawal symptoms usually commence within three hours after the last dose.

Users of daily doses of 1 to 3 grams (1,000–3,000 mg) of meperidine often experience persistent muscular twitches and tremors, hyperactive reflexes, startle responses, agitation, and sometimes seizures and toxic psychosis (including hallucinations).

Other effects resulting from long-term use of meperidine are mild and similar to those produced by most other narcotic analgesics.

LETHALITY

Severe overdose, particularly after intravenous injection, can result in very slow, shallow, and irregular breathing, circulatory collapse, cardiac arrest, and death from respiratory arrest. The lethal dose for a nontolerant adult is estimated to be 1 gram (1,000 mg).

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance to the analgesic effect of meperidine develops more gradually than for most other potent narcotic analgesics. The daily dose of meperidine necessary to produce a consistently effective analgesic result may not need to be increased for several weeks or even months; for this reason it is often the preferred drug for symptomatic relief of moderately severe chronic pain (such as that associated with back injury). However, tolerance to meperidine's euphoric and sedating effects can develop as rapidly as for other narcotic analgesics; therefore, those who abuse the drug for these effects must frequently increase their daily dose. Tolerance to meperidine's respiratory-depressant effects also develops; but even after protracted high-dose use, tolerance to its CNS-excitation effects does not appear to develop.

Physical Dependence/Withdrawal

Physical and psychological dependence can develop with regular use, even at low daily doses. However, severity of dependence increases with chronicity of use and with increasingly higher daily doses. Withdrawal sickness is generally milder and its duration is shorter than for morphine or heroin. Early withdrawal symptoms (as soon as three hours after the last dose) consist of restlessness, muscle twitches, sweating, and anxiety; these peak in intensity between eight and 12 hours later. In some cases the symptoms may be as severe as in morphine withdrawal; but unlike morphine withdrawal, meperidine withdrawal ordinarily does not involve nausea, vomiting, and diarrhea. The intensity of symptoms declines gradually, and they are usually no longer present by the fourth or fifth day.

Psychological Dependence

The profound impact of long-term dependence on meperidine (and other narcotic analgesics) is often observable for a long time after the classical phase of withdrawal sickness has been completed. Depression, anxiety, insomnia, loss of appetite, periods of agitation, and a craving for the drug may persist for extended periods of time. Such symptoms are often reported to be indicative of psychological dependence. However, a purely psychological explanation may be an oversimplification. Much is yet to be understood about the possibly complex physiological adjustments which may result from narcotic analgesic dependence and the fate of these adjustments after withdrawal.

PATTERNS OF USE

Meperidine is one of the two most widely used analgesics for severe pain; the other is morphine. Because of its availability in hospitals, it has frequently been reported as being subject to abuse by hospital personnel. While no definitive data support this assertion, results of surveys of physicians and nurses known to be dependent on narcotic analgesics consistently indicate that meperidine is the most commonly abused drug in this class.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of meperidine is more moderate than that of such narcotic analgesics as morphine and heroin. When administered intravenously, the effects of meperidine are experienced more rapidly than those of morphine, but both its euphoric potency and analgesic potency are considerably less. However, when administered orally, meperidine retains a greater degree of its potency than many other common narcotic analgesics, including morphine and heroin.

Inherent Harmfulness

Because meperidine is highly irritating to local tissue when injected, chronic needle administration can be very painful to the user. Furthermore, when abused in high daily doses, very harmful effects such as agitation, toxic psychosis, and convulsions can occur.

Availability

While commonly used in hospitals (and to a lesser degree by outpatients), meperidine is infrequently encountered on the street. It would appear that the relatively moderate degree of euphoria produced by meperidine and its inherently harmful effects when abused make it less appealing to street users than other narcotic analgesics.

Meprobamate

DRUG CLASS: MINOR TRANQUILLIZER

SYNOPSIS

Meprobamate was the first drug to be labeled a minor tranquillizer. When it was introduced in the mid-1950s, it was marketed as a safe and nonaddicting alternative to the barbiturates and other available sedative/hypnotic drugs. However, many researchers now believe that the distinction between meprobamate and the sedative/hypnotics is artificial; that is, differences between them are thought to be a function of the intensity of their effects rather than of true dissimilarities in the nature of their effects.

At therapeutic low-dose levels, meprobamate is effective in managing a variety of tension and nonpsychotic anxiety states. At moderate dose levels, its anti-anxiety effect is increased, and it can also induce sleep in many users. At such dose levels, the side effects are generally similar to those produced by the barbiturates, although the degree of drowsiness and euphoria generated by meprobamate at equally effective doses tends to be less pronounced. At high doses, the intoxication produced by meprobamate and the barbiturates is almost identical. A major advantage of meprobamate over the barbiturates is that an overdose is far less likely to be lethal. Nonetheless, a number of deaths from meprobamate overdose have occurred, although most have involved the simultaneous consumption of other central nervous system (CNS) depressants.

Tolerance can rapidly develop to the desired effects of meprobamate when it is regularly used. Psychological dependence is common, and mild physical dependence can occur if it is taken daily for extended periods even in therapeutic doses.

Chronic high-dose abuse can produce a state of physical dependence so severe that abrupt abstinence can result in a potentially hazardous withdrawal syndrome.

There has been a notable decline in the prescribing of meprobamate, brought about not only because of the liabilities associated with its use/abuse but also because there are now effective and much safer alternatives, such as the benzodiazepines.[1]

DRUG SOURCE

Meprobamate is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Equanil, Meprospan–400, Miltown.

STREET NAMES

None in common use; however, minor tranquillizers are often referred to as tranks or downers.

COMBINATION PRODUCTS

- 217 Mep (meprobamate, ASA, and caffeine citrate);
- 282 Mep (meprobamate, ASA, caffeine citrate, and codeine phosphate).

MEDICAL USES

For relief of anxiety and tension states, and for promotion of sleep in anxious patients.

PHYSICAL APPEARANCE

Meprobamate occurs as a bitter white powder slightly soluble in water and freely soluble in alcohol.

DOSAGE

Medical

- for anxiety or tension states—400 mg three to four times per day. The daily dose may be increased to a maximum of 2.4 grams (2,400 mg) per 24 hours;

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[1] This family of drugs includes diazepam (e.g., Valium) and chlordiazepoxide (e.g., Librium). See the article Benzodiazepines I.

- for induction of sleep—400–800 mg at bedtime.

Nonmedical

Users may initially take daily doses within the therapeutic range. As tolerance to the desired effects increases, users may take larger daily doses. Highly tolerant abusers have been known to take daily doses up to 10 times the typical daily therapeutic dose, and in some cases even more.

ROUTES OF ADMINISTRATION

Meprobamate is usually taken orally by tablet or capsule. Injection routes have been employed in hospital settings.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, behavioral, subjective: The principal desired effects are feelings of calmness and relaxation; drowsiness may be sufficient to produce sleep. Other effects may include dizziness; lethargy; muscle weakness, mild motor incoordination, impairment of fine motor dexterity; visual disturbances; prickling, tingling, or burning sensations on the skin; numbness; vertigo; sometimes overstimulation or paradoxical excitement.

Cardiovascular: headache; palpitations; slight or sometimes significant drop in blood pressure; mildly irregular heartbeat; sometimes abnormally rapid heart rate.

Gastrointestinal: nausea, vomiting, diarrhea.

Other: in rare cases, allergic reactions.

EFFECTS OF SHORT-TERM USE: MODERATE DOSES[3]

Low-dose effects tend to become more intense. The following effects may also occur at moderate dose levels:

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[2] Single doses of 400 mg or less taken orally by nontolerant users.

[3] Single doses of 800 mg taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

CNS, behavioral, subjective: Sleep induction frequently occurs; however, prior to the onset of sleep, or when sleep does not occur, the user may experience a state similar to mild to moderate alcohol or barbiturate intoxication: euphoria; mild to moderate impairment of cognitive, perceptual, and motor functions; sometimes slurred speech; mild emotional disinhibition; sometimes hostile behavior; mood swings. Marked agitation has occasionally occurred.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[4]

Effects of moderate doses tend to be more intense. The following effects may also occur at high dose levels:

CNS, behavioral, subjective: Induction of deep sleep is the most probable effect; however, prior to the onset of sleep or when sleep does not occur, the clinical picture resembles moderate- to high-dose alcohol or barbiturate intoxication. As the size of the dose increases, there is progressively greater impairment of cognitive, perceptual, and motor functions. The impairment is manifested as heightened activity or oversedation; impairment of both fine and gross motor dexterity; concentration difficulties and impairment of short-term memory; increasingly intense euphoria, or emotional depression or hostility, or (possibly) extreme mood swings; impaired judgment and (possibly) confusion.

Cardiovascular: Hypotensive crisis—that is, rapid and extreme drop in blood pressure—has occasionally occurred.

Respiratory: mild to moderate respiratory depression.

Very high doses (i.e., overdose) can result in deep sleep progressing to stupor or coma and abnormally low blood pressure. Moderate respiratory depression occurs but is generally not nearly as severe as with barbiturate overdose.

EFFECTS OF LONG-TERM USE

Meprobamate tends to be slowly eliminated from the body.

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[4] Single doses in excess of 800 mg taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

Therefore, some patients taking therapeutic doses for protracted periods, as well as many chronic high-dose abusers, may exhibit a state of chronic intoxication, which can be manifested as lethargy, cognitive and motor impairment, slurred speech, memory impairment, confusion, apathy or emotional instability, sleep disturbances, and other forms of impairment similar to those associated with chronic barbiturate intoxication.

LETHALITY

Extreme overdose of meprobamate results in severe coma with lack of responsiveness to intense stimuli and absence of pupillary and other reflex responses. Respiratory depression, accumulation of fluids in the lungs, cardiovascular collapse, heart failure, and occasionally grand mal seizures can also occur. Death has resulted from doses as small as 12 grams (12,000 mg); however, people have been known to survive and recover from doses as great as 40 grams. Although there have been numerous accidental overdoses and suicide attempts involving meprobamate, the actual number of deaths caused by meprobamate taken alone is relatively low, for very large quantities are usually necessary for death to result. However, when the meprobamate overdose is taken in combination with other CNS-depressant drugs, the risk of death is enhanced.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance develops rapidly to the anxiety-relieving and sleep-inducing effects of meprobamate when it is taken on a regular basis, even when the daily doses are within the therapeutic range. Tolerance can also develop quite rapidly to the barbiturate-like euphoria it produces. Therefore, if the user wishes to maintain the original level of intensity of any of the desired effects, it is necessary to increase the size of the daily dose. Abusers tend to increase the size of their daily dose frequently.

There is a high degree of cross-tolerance between meprobamate and sedative/hypnotic drugs such as the barbiturates: that is, once tolerant to a given effect produced by meprobamate, the user will also be tolerant to the same effect produced by an equivalent dose of these other drugs.

Psychological Dependence

Psychological dependence on meprobamate can develop irrespective of the size of the daily dose taken and even when the drug is not used on a daily basis. Psychological dependence on meprobamate is characterized by a craving for its psychological effects, which results in its taking on a magnified importance in the daily life of the user. The psychologically dependent user is quite likely to be unwilling to discontinue use of meprobamate even when the drug no longer produces any significant psychoactive effects, and if the drug is temporarily unavailable, anxiety or even feelings of panic might ensue.

Physical Dependence/Withdrawal

Chronic daily use of meprobamate in doses greater than 2.4 grams (2,400 mg) often results in a state of physical dependence; in fact, it has been reported that for some users, a daily dose as small as 1.6 grams can cause mild physical dependence when it is taken on a regular basis for extended periods of time. Generally, however, the greater the size of the daily dose and the longer the period of use/abuse, the more severe is the withdrawal sickness resulting from abrupt abstinence.

The onset of withdrawal sickness usually occurs within 24–36 hours after the last dose. The syndrome can range from such relatively mild and temporary symptoms as restlessness, anxiety, and insomnia in mildly dependent users to potentially life-threatening complications in severely dependent users. In addition to the aforementioned symptoms, mild withdrawal sickness characteristically includes muscle twitching, motor incoordination, tremors, loss of appetite, and nausea and vomiting. In severely dependent users (i.e., taking several grams of meprobamate per day) mild withdrawal symptoms may be greatly intensified, and the following can also occur: severe agitation, hallucinations, and tremors resembling alcoholic delirium tremens, and sometimes grand mal seizures and coma. These severe symptoms also occasionally occur in physically dependent users of smaller daily doses. Death has been reported to occur during severe withdrawal.

Because there is a substantial degree of cross-dependence between meprobamate and such sedative/hypnotics as the barbiturates, phenobarbital has been used in medical settings to withdraw dependent patients gradually. The procedure involves the initial administration of suitably large daily doses of phenobarbital and then a progressive reduction in the size of the doses.

PATTERNS OF USE

When meprobamate was introduced in the mid-1950s, it almost immediately became the drug of choice for the pharmacological treatment of anxiety and tension. It was widely endorsed as a much safer and nonaddicting alternative to the barbiturates. In fact, it was reported to be so popular that, for a while, the demand exceeded the available supply for legitimate users. Meprobamate also rapidly became widely popular among drug abusers because of its capacity to produce barbiturate-like euphoria. It was frequently taken in combination with sedative/hypnotics such as alcohol or barbiturates, as well as with heroin. Users claimed that the combinations produce an even greater degree of euphoria than either drug taken alone. In addition, many of those taking meprobamate under medical supervision misused this drug to combat even the natural minor stresses of daily life, and therefore inadvertently became dependent on it.

Much of the widespread popularity of meprobamate resulted from a concerted campaign to convince physicians and the public that it was the first of a new class of drugs, minor tranquillizers, that would be at least as effective as the barbiturates in managing anxiety and yet would have only negligible side effects at therapeutic doses. This early enthusiasm about its merits was not well supported by research and clinical evidence. Its use has greatly declined since its peak popularity in the mid-1960s for reasons which are explored below.

ABUSE POTENTIAL

Dependence Liability

The effects of meprobamate are in many respects quite similar to those of the barbiturates. Meprobamate is rapidly absorbed from the gastrointestinal tract, and when taken in sufficient quantities it produces a state of pleasurable intoxication resembling that produced by most sedative/hypnotic drugs. It has clearly demonstrated its capacity to produce severe physical dependence; furthermore, undoubtedly a large number of users were psychologically dependent on meprobamate during the period of its peak popularity.

Inherent Harmfulness

Overdose of meprobamate taken alone is far less lethal than an overdose of barbiturates; however, fatalities have occurred. A greater number of deaths have resulted when meprobamate has been combined with other CNS-depressant drugs. Serious cardiovascular side effects can occur even when the drug is taken at daily doses within the therapeutic range. The withdrawal sickness produced by abrupt abstinence after chronic high-dose abuse can present dangerous complications.

Availability

There has been a marked decline in the use of meprobamate for the above reasons and because of the introduction of the benzodiazepines (e.g., diazepam and chlordiazepoxide—Valium and Librium respectively); the latter drugs are effective in controlling anxiety and tension, and do so with fewer and milder side effects.

Mescaline

DRUG CLASS: HALLUCINOGEN

SYNOPSIS

Mescaline is a naturally occurring hallucinogen which is derived from the Mexican peyote cactus and the San Pedro cactus found in Peru and Ecuador. This drug produces a spectrum of effects similar to those of LSD and psilocybin, including vivid visual "pseudohallucinations" and distortions (which are known to the user to be unreal) and synesthesias (the paradoxical melding of the senses so that, for example, music may appear to be "seen"). Alterations in the perception of time, space, and body image can also frequently occur.

The individual's emotional response to these psychic effects may range from joy and exhilaration to extreme anxiety and even terror. There is no way to accurately predict how any user will react on any given occasion to mescaline. Even seasoned users who usually experience the desired effects may on other occasions experience intense distress.

Mescaline has been used for centuries for its alleged propensity to induce profound mystical experiences. At present, only members of the Native American Church may use it legally.

The legendary reputation of this drug is the principal reason for the widespread practice on the street of selling other drugs such as PCP (phencyclidine) or LSD as mescaline; in actuality, mescaline is rarely found outside Mexico and the southwestern United States.

DRUG SOURCE

Mescaline naturally occurs in the peyote cactus, *Lophophora williamsii*, found in Mexico and parts of the southwestern United States, and the San Pedro cactus, found in Peru and Ecuador. It can also be produced in a laboratory by chemical synthesis.

TRADE NAMES

Not applicable.

DRUG COMBINATIONS

1. Peyote buttons, which contain mescaline, also contain more than a dozen other alkaloids; among these are a respiratory stimulant, a reflex excitant, and a convulsant.
2. A combination of mescaline, LSD, and cannabis has occasionally been used in some areas of North America. Its street name is TMA.[1] (Trimethoxyamphetamine, a synthetic hallucinogen, is also referred to as TMA.)

MEDICAL USES

There is no current medical use for mescaline. In the past researchers have explored the possibility of its use in facilitating psychotherapy.

PHYSICAL APPEARANCE

In its pure form mescaline sulfate is a white crystalline material. Synthetic mescaline often appears as white or colored powder. "Organic" or "natural" mescaline is the name sometimes used to describe dried, ground peyote buttons, which are usually distributed in capsule form. On the street, however, preparations alleged to be natural mescaline have almost invariably been found to be something else, such as LSD and/or PCP.

ROUTES OF ADMINISTRATION

1. Mescaline is most frequently administered orally in the form of a powder, tablet, capsule, or liquid. Peyote buttons, although very unpleasant to taste, can be chewed to obtain the desired effects.
2. Peyote buttons are sometimes ground and smoked with a leaf material, such as cannabis or tobacco.

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[1] "TMA" is so named for THC (tetrahydrocannabinol, mescaline, and acid (LSD).

3. Mescaline can be injected in solution, but this route is used much less frequently than the oral route.

DOSAGE

Medical

Not applicable.

Nonmedical

The usual oral dose of mescaline ranges between 300 and 500 mg (approximately equivalent to the amount contained in three to six peyote buttons). This dose level will produce effects roughly similar to 50–100 micrograms (0.05–0.1 mg) of LSD or 10 mg of psilocybin.

EFFECTS OF SHORT-TERM USE[2]

CNS, behavioral, subjective: Mescaline produces a fairly wide variation between different users in possible perceptual, cognitive, and emotional experiences. Drug effects are influenced by the size of the dose, the setting, the user's expectations, past drug experiences, and personality. It is not unusual for the user to experience differing reactions to mescaline during different drug-taking episodes. Early somatic effects[3] which can occur include numbness, tension and anxiety, rapid reflexes, muscle twitches and muscle weakness, motor incoordination, tremulousness, dizziness, and pupillary dilation. Later effects can include the following:

1. There may be vivid perceptual distortions, primarily visual, such as "pseudohallucinations" and "pseudoillusions." Often the user "sees" brightly colored lights, geometric patterns, animals, or occasionally humans.

2. Perception of time may be distorted (minutes may seem to pass as slowly as hours).

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[2] 300–500 mg taken orally by nontolerant users. The chemical structure of mescaline bears resemblance to norepinephrine and amphetamines; at hallucinogenic doses the somatic symptoms produced by mescaline are similar to those produced by small amounts of these substances. At higher doses there may be reduced blood pressure, heart rate, and respiratory rate. Psychic effects at higher doses tend to be more intense.

[3] Occurring within the first hour after administration.

3. Perception of space may be distorted.
4. Body image may be distorted. There may be sensations of heaviness and being pulled down by gravity or of weightlessness resulting in a feeling of floating.
5. Synesthesias frequently occur.
6. There may be a partial or complete loss of recognized boundaries between self and the environment, reactions to which may range from intense pleasure to terror.
7. All sensory experiences tend to be heightened: the user perceives brighter colors, sharper definition of objects, increased hearing acuity, more sharply distinguished taste, etc. These heightened experiences may alternate with sensory impairment.
8. Difficulties in concentrating, thinking, and maintaining attention are often experienced.
9. While memory may also be impaired, it is not unusual for past and possibly repressed experiences to be vividly recalled and sometimes melded with current experiences; however, a sense of the present reality (the "here and now") may be temporarily lost.
10. There may be preoccupation with otherwise trivial thoughts, experiences, or objects, which take on magnified importance.
11. Users may feel that they are undergoing a profound mystical, religious, or "cosmic" experience—for many users perhaps the most desired effect.
12. A highly adverse reaction can occur in some users (a "bad trip") and may be characterized by the following symptoms: frightening hallucinations, confusion, disorientation, fear of nonexistence or disintegration of self, inability to distinguish between reality and unreality, paranoid thinking, possibly severe agitation and/or depression, and panic or even terror.

Cardiovascular: increased blood pressure and heart rate; elevated body temperature and sweating, which may alternate with chills and shivering (all are early effects).

Gastrointestinal: Intense nausea and vomiting are extremely common; suppression of appetite (all are early effects).

Psychic effects are experienced within 1–2 hours and gradually disappear 10–12 hours after administration.

EFFECTS OF LONG-TERM USE

Chronic everyday use of mescaline is a pattern which is very unlikely to occur (see below: Tolerance and Dependence).

Animals subjected to regular administration of mescaline have shown an increased risk of birth defects in their offspring. However, preliminary research on the frequency of chromosomal abnormalities in Mexican Indians has not found any significant differences between those who traditionally use peyote and those who do not (Dorrance et al., 1975).

Mescaline has occasionally precipitated a protracted psychotic state similar to paranoid schizophrenia. However, some observers have suggested that this is likely to occur only in those users who were latent psychotics prior to the psychosis-inducing event.

LETHALITY

While very high doses of mescaline can produce severe, but temporary, sensory disturbances, there have been no reports of life-threatening effects directly attributable to the drug. (However, PCP or PCP/LSD combinations are frequently sold as mescaline; these in severe overdose can result in death.)

TOLERANCE AND DEPENDENCE

Upon repeated daily administrations of hallucinogenic doses of mescaline, tolerance to its effects can develop rapidly, ordinarily within three to six days.[4] Cross-tolerance to such other hallucinogenic drugs as LSD and psilocybin also occurs; without a period of abstinence from mescaline or these other drugs, no amount of any of them will produce the desired psychic effects. After several days of abstinence, however, the desired sensitivity is restored.

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[4] See Tolerance—Tachyphylaxis under Drug Tolerance: The Body's Adaptation to Drugs in section 1.

There is at present no evidence of physical dependence (i.e., of withdrawal phenomena upon cessation of use). While psychological dependence is possible, it has not been reported.

PATTERNS OF USE

Mescaline is a name frequently mentioned on the street drug market, but there is rarely any real mescaline available in most areas of North America. Drug-analysis results in Canadian and U.S. laboratories reveal that an overwhelming percentage of alleged mescaline samples are actually such other drugs as PCP or PCP/LSD combinations.

Mescaline ingestion in the form of peyote is a sacrament of the Native American Church of North America, which claims approximately a quarter of a million members of Indian ancestry in the United States and Canada. This mescaline sacrament is legal in the United States and is the only legally approved use of any of the major hallucinogenic drugs at this time in North America other than for research purposes.

ABUSE POTENTIAL

Dependence on mescaline is not known to occur, and whatever harm the drug may cause does not appear to be a significant deterrent to its use.[5] However, as the drug is rarely available in our society, its abuse potential is at this time extremely low.

REFERENCE

Dorrance, D.L., Janiger, O., and Teplitz, R.L., Effect of peyote on human chromosomes, *Journal of the American Medical Association*, 234: 299-313, 1975.

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[5] Nonetheless, there is some danger of a psychotic reaction in a small percentage of users.

Methadone

DRUG CLASS: NARCOTIC ANALGESIC; OPIOID

SYNOPSIS

Methadone is a synthetic narcotic analgesic similar in potency to morphine. However, it has certain advantages over other powerful drugs in this class, such as morphine and heroin: (1) its effects are longer lasting, and therefore methadone can be administered less frequently; (2) it is also highly effective when orally administered, and therefore it is more convenient to use. The latter property makes methadone less harmful with regard to initiating and reinforcing the ritual-like habits related to needle administration of drugs. Both factors explain why methadone is widely used in the treatment of narcotic analgesic dependence. In methadone maintenance programs a methadone preparation for oral consumption is substituted for heroin or other illicitly used narcotic analgesics, so as to allow dependent users to achieve relatively more productive and less deviant lifestyles.

Unfortunately, methadone also has a high dependence liability. In the past it was subject to widespread abuse, and many deaths among street users were attributed to methadone overdose. Nowadays very strict controls—over the production of methadone preparations which are difficult to dissolve for injection, and over their distribution—seem to have resulted in considerably less street abuse. However, because even oral preparations of methadone can suppress withdrawal sickness from heroin (or other powerful narcotic analgesics) if taken in sufficient amounts, they continue to retain some value to the street drug abuser.

DRUG SOURCE

Methadone is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

In Canada it is marketed under its nonproprietary name.

STREET NAMES

Dollies (from the trade name Dolophine under which it is marketed, although not in Canada); meth.

COMBINATION PRODUCTS

An experimental oral combination containing methadone and a narcotic antagonist[1] has been tested in clinical trials. When the combination is taken orally, the narcotic antagonist is ineffective; but when it is injected, the narcotic antagonist almost immediately precipitates a withdrawal reaction. This product is designed to be useless to suppliers who service the street-market demand for injectable methadone.

Methadone has occasionally been encountered on the illicit market in tablets containing acetylsalicylic acid (ASA).

MEDICAL USES

- a substitute drug in narcotic analgesic dependence therapy;
- a long-acting analgesic for moderately severe to severe pain.

PHYSICAL APPEARANCE

In pure form methadone is a white crystalline powder which is soluble in water and freely soluble in alcohol. When used in narcotic analgesic dependence programs it is usually dissolved in an orange-flavored beverage.

DOSAGE

Medical

In Canada, under highly restricted circumstances, methadone may be clinically employed for its analgesic properties. The single orally administered dose range is 5–15 mg; the subcutaneous injection range is usually 5–10 mg.[2]

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[1] See Naloxone article below.

[2] Analgesic potency compared to morphine, when both are administered by subcutaneous injection: 7.5–10 mg methadone is equivalent to 10 mg morphine.

METHADONE MAINTENANCE PROGRAMS

Initial daily dose is typically 20–40 mg, orally and in divided doses. Daily dose is gradually increased, as tolerance develops, until a stabilization (or maintenance) dose level is achieved. Thereafter, the patient is typically maintained on a single daily oral dose at the stabilization level and without further increases (the typical range is 40–100 mg/day). In Canada, methadone may be prescribed only by medical practitioners who have received special authorization from the Health Protection Branch, Health and Welfare Canada. (The relative advantages of substituting methadone for other drugs in this class in the treatment of narcotic analgesic dependence are discussed below.)

Nonmedical

The nontolerant person receiving the drug by subcutaneous injection may experience pleasurable sensations from doses of less than 5 mg; under controlled experimental conditions subcutaneous doses administered to tolerant individuals have been as great as 100 mg four times per day. Tolerant street users may take even higher doses.

ROUTES OF ADMINISTRATION

Primarily orally and by subcutaneous injection. Abusers prefer intravenous injection.

EFFECTS OF SHORT-TERM USE: LOW DOSES[3]

CNS, behavioral, subjective: suppression of the sensation of and emotional response to pain; euphoria or anxiety; lightheadedness, dizziness; sedation, relaxation; weakness; drowsiness; pupillary constriction, impaired visual acuity, impaired night vision.

Cardiovascular: sweating; flushing; slight drop in body temperature.

Respiratory: slightly reduced respiratory rate.

Gastrointestinal: nausea and vomiting; constipation; suppression of appetite; dry mouth.

Other: reduced libido; itchy skin; urinary retention.

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[3] Single doses 2.5–15 mg in nontolerant users by subcutaneous injection up to 45 mg per day.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[4]

Intensification of low-dose effects may occur. Duration of effects increases with progressively higher doses. As the dose increases (1) sensitivity and emotional response to painful stimuli decrease; (2) there is a greater probability of sleep; (3) ability to concentrate is progressively impaired; (4) breathing becomes progressively slower and more shallow; (5) heart rate gradually slows and blood pressure decreases.

At very high doses (i.e., overdose) there is markedly shallow and slow breathing, deep sleep possibly progressing to stupor or coma, pinpoint pupils, cyanosis, flaccidity of skeletal muscles, low blood pressure, slow heart rate, and cold and clammy skin.

EFFECTS OF LONG-TERM USE

In North America, the principal clinical use of methadone is in the treatment of persons physically dependent on narcotic analgesics. Designated treatment facilities, under special licence, provide dependent users with methadone as a substitute for such other illicitly used narcotic analgesics as heroin, morphine, or oxycodone (e.g., Percodan). Users can be maintained on methadone for extended periods of time. In most programs, daily doses of methadone are gradually reduced; this procedure is designed to help the dependent person to achieve a drug-free state without suffering the distress of abrupt withdrawal.

Methadone was selected for North American programs as the most appropriate drug because it possesses several important advantages over most other narcotic analgesics:

1. Methadone is sufficiently potent to suppress the withdrawal symptoms of other powerful narcotic analgesics.[5]
2. In many users it can also suppress chronic "drug hunger" (intense craving) for these other drugs. Some clinicians and researchers believe "drug hunger" to be the major reason why many dependent users relapse after periods of abstinence. With methadone use, tolerance to this effect does not appear to develop.

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[4] Doses above the medically recommended level in nontolerant users, or lower doses in particularly sensitive individuals.

[5] A result of the high degree of cross-dependence among narcotic analgesics.

3. Unlike many other powerful narcotic analgesics, methadone administered orally retains much of its efficacy but does not produce euphoria in those users already tolerant to the euphoric effect of other powerful narcotic analgesics.[6]
4. Its effectiveness when administered orally helps to extinguish gratification previously associated with needle administration.
5. Methadone has a longer period of action than most other common powerful narcotic analgesics, and therefore can be administered less frequently. In most cases a single dose (usually ranging between 40 and 120 mg) is sufficient.
6. Long-term maintenance on methadone does not appear to produce any significant health problems other than physical dependence.

For these various reasons, long-term methadone maintenance has helped many dependent individuals to a more productive and less antisocial lifestyle.[7]

There are, however, some unpleasant side effects directly associated with chronic methadone use. These may include constipation, pupillary constriction which may impair night vision, blurred vision, excessive sweating, reduced libido, menstrual irregularity, urinary retention, occasionally pains in the joints and bones, sleep disturbance, and certain types of respiratory impairment.

LETHALITY

Severe overdose, particularly by intravenous injection, can produce coma, cyanosis, pinpoint pupils, severe respiratory depression, and circulatory collapse; death usually results from respiratory arrest, and in some cases cardiac arrest. The minimum lethal dose in non-tolerant adults is estimated to be 75 mg. Doses as small as 10 mg have been reported to be fatal to children.

TOLERANCE AND DEPENDENCE

Tolerance

When taken regularly in high doses by abusers, tolerance to the euphoric, analgesic, and sedating effects can develop rapidly (i.e., within one to two weeks substantial tolerance occurs); users must increase their daily dose to maintain, but not necessarily intensify, the subjectively pleasurable experiences. Tolerance develops for other effects of methadone, but more gradually than for morphine; these include nausea, loss of appetite, pupillary constriction, and particularly respiratory depression. Partial tolerance develops to methadone's constipating effects.

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[6] A result of the high degree of cross-tolerance among narcotic analgesics.

[7] Methadone maintenance programs are not without critics. Their criticisms are discussed in the Narcotic Analgesics chapter in section 2.

Physical Dependence/Withdrawal

Chronic high-dose use can lead to powerful physical and psychological dependence. Since methadone is excreted more slowly from the body than morphine, the brain has more time to adapt to the drug-free state. Therefore, withdrawal sickness tends to be less severe than for morphine, onset is later, and the course is more protracted.

Early symptoms (after abrupt rather than gradual termination of use) are usually not observed until 24–48 hours after the last dose. They include: loss of appetite, insomnia, abdominal pain, alternations between flushing and chills, excessive sweating, headache, and pains in muscles and bones. Nausea, vomiting, and increases in body temperature, blood pressure, pulse, respiratory rate, and pupillary size also occur. Intensity of symptoms peaks at 72 hours after the last administration and typically does not substantially diminish for at least two weeks. The syndrome very gradually declines, and overt symptoms are no longer present by about the sixth or seventh week.

Gradual withdrawal (through periodic small reductions in daily dose) in methadone maintenance/withdrawal programs may take several months, and in some programs up to a year.

Psychological Dependence

After withdrawal from methadone is completed, a craving for narcotic analgesics is often experienced and may persist indefinitely. In addition, many former users complain of tiredness, weakness, sleep disturbances, and anxiety and/or depression. Such symptoms are often thought to be indicative of psychological dependence. However, such an explanation may be an oversimplification; much is yet to be understood about possibly complex physiological adjustments which may result from narcotic analgesic dependence and the fate of these adjustments after withdrawal.

PATTERNS OF USE

In the early 1970s abuse of methadone via intravenous injection in the core of large American cities was extremely high. The number of deaths believed to be related to methadone abuse in New York City in 1973 actually exceeded the number of deaths attributed to heroin abuse; however, with more stringent control over distribution and the greater use of methadone preparations which make injection very difficult, widespread street abuse substantially diminished. Nevertheless, because of its considerable effectiveness in suppressing withdrawal from other narcotic analgesics, methadone is still valued on the street.

It is estimated that there are more than 90,000 persons in North America who take methadone under medical supervision in maintenance or gradual-withdrawal programs. In spite of criticisms regarding methadone maintenance, at this time there are few other viable legal alternatives available to narcotic analgesic dependent people.

ABUSE POTENTIAL

Dependence Liability

Methadone in its pure form possesses a dependence liability similar to that of morphine.[8] This reflects both its euphoric and analgesic properties and its solubility. The high fat solubility of methadone permits immediate and intense gratification, for the drug enters the brain very rapidly after intravenous injection.

Inherent Harmfulness

In low to moderate doses methadone ordinarily does not produce hazardous effects. However, nausea and vomiting are common, and the user must be willing to continue using the drug until tolerance to these side effects develops. In the past, when methadone was more easily available to street users in injectable preparations, many deaths were attributed to methadone overdose.

Availability

In Canada only specially authorized physicians can prescribe methadone. Currently available legal preparations used in methadone maintenance programs contain insoluble substances which make injection very difficult.

[8] When each drug is injected subcutaneously, experimental subjects report an intensity of euphoria similar to that of morphine.

Methaqualone

DRUG CLASS: SEDATIVE/HYPNOTIC

SYNOPSIS

Methaqualone is one of a number of sedative/hypnotic drugs to be synthesized during the past few decades. It was originally promoted as a safer and nonaddictive alternative to the barbiturates. At low therapeutic doses, it produces sedation and its side effects tend to be few and mild. At higher therapeutic doses, it induces sleep; however, before the user falls asleep or if the user does not fall asleep, side effects tend to be both more pronounced than at lower doses and similar to those produced by the barbiturates.

Abusers of methaqualone claim that this drug produces a mellow and pleasurable "high," often accompanied by a desire for close interpersonal contact and by sexual arousal; for these reasons, methaqualone rapidly achieved wide popularity among street drug abusers in many areas of the world. The sexual arousal attributed to methaqualone does not appear to be caused by any real aphrodisiac properties inherent in the drug; rather, it results from a depression of the emotional inhibitory centres in the brain. (A similar disinhibition is produced by alcohol and other sedative/hypnotic drugs.) In fact, at high dose levels of methaqualone, the sexual ability of most males is diminished.

With regular use, tolerance develops rapidly to the sedative, sleep-inducing, sleep-maintaining, and euphoric properties of methaqualone. Chronic high-dose abuse can cause profound barbiturate-like physical dependence, and abrupt abstinence often produces psychotic symptoms and potentially life-threatening seizure activity. Acute overdose can also result in potentially fatal seizures, although respiratory depression is usually not as severe as with most other sedative/hypnotic drugs. Most overdose deaths implicating methaqualone also involve simultaneous consumption of alcohol, and under these conditions death typically results from respiratory arrest.

DRUG SOURCE

Methaqualone is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Mequelon, Sedalone, Triador. (Quāalude and Sopor are not available in Canada.)

STREET NAMES

Love drug, ludes, quads, pillow.

COMBINATION PRODUCTS

Mandrax (methaqualone and diphenhydramine[1]); street names for Mandrax include mandrakes and mandies.

MEDICAL USES

For daytime sedation and for induction of sleep.

PHYSICAL APPEARANCE

Methaqualone occurs as white crystals, very slightly soluble in water and in alcohol.

DOSAGE

Medical

- for daytime sedation—75 mg up to four times per day after meals and at bedtime;
- for sleep induction—150–300 mg before bedtime.

Nonmedical

Users may initially take daily doses which are within the therapeutic range. With increased tolerance to the sleep-inducing and/or pleasurable effects, daily doses may then be increased. It is not unusual for tolerant abusers to take 1–2 grams (1,000–2,000 mg) per day. Highly tolerant abusers have been known to take even larger doses.

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[1] Diphenhydramine is an antihistamine.

ROUTES OF ADMINISTRATION

Methaqualone is taken orally by tablet or capsule. Abusers have occasionally injected this drug; however, when it is administered intravenously on a regular basis, abscesses and cellulitis characteristically occur at the sites of injection. It has been reported that some abusers smoke methaqualone either by itself (in a small pipe) or sprinkled on marijuana cigarettes.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, behavioral, subjective: The principal desired effects are feelings of calmness and relaxation; for some there may be drowsiness possibly sufficient to produce sleep. Some may experience dizziness, fatigue, or lethargy; others may experience restlessness, anxiety, and prickling, tingling, or burning sensations or numbness of the extremities.

Cardiovascular: headache, perspiration.

Gastrointestinal: dry mouth, loss of appetite, nausea and vomiting, stomach discomfort, and diarrhea.

Other: Hangover may occur after the effects of the drug begin to wear off.

EFFECTS OF SHORT-TERM USE: MODERATE DOSES[3]

Low-dose effects tend to become more intense. The following effects may also occur at moderate dose levels:

CNS, behavioral, subjective: induction of sleep (however, a few consecutive nightly administrations may be necessary before this desired effect occurs). Prior to the onset of sleep or when sleep does not occur, the user may experience euphoria, increased sociability and self-confidence, reduced inhibitions, tingling sensations or numbness throughout the body, and mild impairment of motor coordination and of cognitive processes; sexual arousal is often reported.

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[2] Single doses of approximately 75 mg taken orally by nontolerant users.

[3] Single doses of 150–300 mg taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[4]

The effects produced by low to moderate doses tend to become more intense. The following effects may also occur at higher dose levels:

CNS, behavioral, subjective: A mellow, sensual, and dissociative "high," reportedly similar to that produced by heroin, is a key effect desired by the high-dose user. However, a nontolerant user may be overcome by drowsiness and sleep. Other effects which may precede sleep, when it occurs, include a general numbness or tingling sensation throughout the body, motor incoordination, slurred speech, muscle weakness, weakness of the knees and ankles, tremors, muscle spasms, restlessness, and sometimes disorientation and a fear that one is "losing one's mind," which may result in severe agitation or panic. Amnesia for events during the drug-taking episode sometimes occurs.

Cardiovascular: profuse perspiration; chills; abnormally rapid heart rate.

Respiratory: mild to moderate respiratory depression.

These effects tend to disappear within six to eight hours after administration, although some users continue to experience several of the effects for up to 24 hours, or, in a few instances, longer. The longer-lasting effects include disorientation, continued fear of "losing one's mind," dizziness, headache, and hangover.

At higher doses, the respiratory depression produced by methaqualone is usually not as great as that produced by the barbiturates and most other sedative/hypnotics.

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[4] Single doses in excess of the therapeutic range taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

EFFECTS OF LONG-TERM USE

At lower sleep-inducing doses (i.e., 150 mg) methaqualone does not appear to reduce REM sleep—those recurring phases of sleep characterized by rapid eye movement, constant dreaming, and extreme muscle relaxation. However, evidence of the effects of methaqualone on REM sleep at higher therapeutic doses (i.e., 300 mg) is contradictory and requires further investigation.

Reliable information regarding the effects of long-term exclusive abuse of this drug has not yet been reported. However, it is generally acknowledged that the effects are probably similar to those produced by long-term abuse of barbiturates, such as impairment of cognitive and motor functions, visual disturbances, emotional instability, sleep dysfunctions including frequent insomnia, and fatigue.

High-dose abuse of the combination drug Mandrax[5] (i.e., 400–1,600 mg of methaqualone) has sometimes induced an acute toxic psychotic state characterized by delusions, hallucinations, disorientation, and confusion. This state usually disappears within two to three days provided that no additional doses are taken.

LETHALITY

Severe acute overdose of methaqualone tends to produce muscle spasms, abnormally rapid reflexes, extreme muscle tension, and restlessness. Grand mal seizures, delirium, and coma often rapidly ensue. Spontaneous vomiting and secretion of fluids in the lungs usually occur and can result in such complications as serious breathing difficulties or obstruction of the respiratory pathway. Other symptoms can include liver and kidney impairment, accumulation of fluids in the cutaneous blood vessels, abnormally rapid heart rate, and bleeding. When taken by itself, overdose of methaqualone is less dangerous than barbiturate overdose in terms of severe respiratory depression and cardiovascular depression; nonetheless, shock and/or respiratory arrest do occasionally occur. Coma has resulted from overdoses averaging 2.4 grams (2,400 mg) of methaqualone, and death has resulted from ingestion of as little as 8 grams; however, some patients have survived overdoses of as much as 22 grams. Most reported fatalities have occurred when the methaqualone overdose was combined with consumption of alcohol; such a combination tends to cause severe respiratory depression and death from respiratory arrest.

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[5] A single therapeutic dose of Mandrax contains 250 mg of methaqualone and 25 mg of diphenhydramine.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance to the sleep-inducing and sleep-maintaining effects of methaqualone can rapidly develop with nightly use, often within a few weeks; however, there is evidence of considerable individual differences in the rate at which tolerance to these effects is acquired. Most investigators agree that tolerance also rapidly develops to the euphoria-producing effects. Therefore, to maintain any of these effects at the original level of intensity, users must increase their regular dose; for long-term abusers, such increases may be required on several occasions.

There appears to be a considerable degree of cross-tolerance between methaqualone and most other sedative/hypnotics, in spite of the structural dissimilarities between methaqualone and other members of this class of drugs. Thus, once tolerant to the effects of methaqualone at a given dose level, the user will also be tolerant to the sedative effects produced by other sedative/hypnotics in equally potent doses.

Psychological Dependence

Psychological dependence on methaqualone may develop irrespective of the size of the regular dose taken and even when the drug is not used on an everyday basis. Psychological dependence is characterized as the craving for the psychological effects of the drug and a preoccupation with it so great that it takes on highly magnified importance in the life of the user. Anxiety or even feelings of panic may occur if the drug is temporarily unavailable. Psychologically dependent users resist discontinuing the use of methaqualone even when it no longer produces any significant psychoactive effects.

Physical Dependence/Withdrawal

Physical dependence on methaqualone can develop as a result of chronic high-dose abuse. A mild withdrawal sickness occurs after abrupt abstinence from moderately high daily doses (i.e., 1 gram or less). Symptoms appear within one to three days after the last dose and may last for several days; they include restlessness, irritability, insomnia, anxiety, headache, loss of appetite, nausea and vomiting, abdominal pain, muscle twitches, and mild tremors. A more severe withdrawal sickness occurs upon abrupt abstinence after extended periods of very-high-dose abuse (i.e., 1.5–2.0 grams per day or more for several months). The syndrome involves an intensification of the above symptoms and can also include mental confusion, delirium, hallucinations, dangerously high body temperature, and potentially lethal generalized seizure activity.

Because there is a substantial degree of cross-dependence between methaqualone and most other sedative/hypnotics, withdrawal sickness can be substantially suppressed by the administration of any of several other drugs in this class. In medical settings, the severity of the withdrawal symptoms is often mitigated by the administration of phenobarbital, initially in high doses and then in gradually reduced daily doses. A combination of phenytoin (e.g., Dilantin) and either chlorpromazine or diazepam has been reported to be effective in controlling the more severe symptoms of methaqualone withdrawal sickness.

PATTERNS OF USE

Abuse of methaqualone during the 1960s reached epidemic proportions in Great Britain, Germany, and Japan. More recently, the drug has gained widespread popularity in the United States. However, evidence on abuse in Canada suggests that methaqualone has not become as popular in this country as it has elsewhere.

In Great Britain, Mandrax was introduced in 1965 mainly as an alternative for those who manifested allergic reactions to barbiturates and chloral hydrate. It was marketed as a drug which did not produce physical dependence. Within three years (i.e., by 1968), methaqualone had become the most widely prescribed sedative/hypnotic drug in that country. In the United States, during the late 1970s almost as many prescriptions were written for methaqualone as for one of the most widely used barbiturates, secobarbital (e.g., Seconal)—1.4 million and 1.5 million prescriptions respectively in the year 1977.

Methaqualone seems to be particularly popular with students, who often combine it with alcohol—a hazardous practice. They allege that the combination produces greater euphoria than when either is taken alone. Methaqualone is also widely used by heroin addicts who are tolerant to the generally diluted heroin available on the streets; they combine methaqualone with the weak heroin and intravenously inject the mixture in order to achieve a rewarding "high." Methaqualone is also favored by methadone clinic clients, because it is not as easily detected as the barbiturates in urine screening. Regular abuse of any of these drug combinations can give rise to a complex state of simultaneous drug dependence.

Many observers have suggested that the rapid rise in popularity of methaqualone is primarily due to (1) the widely held misapprehension that methaqualone can produce a physiological state of sexual stimulation and (2) the peaceful “high” achieved by many users. With regard to the former reason, there is no evidence that this drug possesses any aphrodisiac properties. Rather, as with alcohol and other sedative/hypnotic drugs, the temporary increase in libido is likely due to the depression of those brain centres which inhibit emotional feeling and expression.[6] In fact, when methaqualone is taken at higher doses, the sexual ability of most males diminishes.

ABUSE POTENTIAL

Dependence Liability

Methaqualone can rapidly produce intense euphoria even when taken orally; this highly pleasurable state can be achieved within 15–20 minutes after ingestion. Methaqualone would therefore appear to possess a dependence liability similar to that of the short-acting barbiturates, such as secobarbital or pentobarbital.

Inherent Harmfulness

In contrast to most other widely used sedative/hypnotic drugs, very high doses of methaqualone do not typically produce potentially dangerous levels of respiratory depression. However, overdoses can produce such hazardous consequences as grand mal seizures, and when overdoses have been taken in combination with other sedative/hypnotic drugs, a number of deaths from respiratory arrest have occurred. Nonetheless, methaqualone does not appear to have achieved the level of notoriety as a dangerous drug that is accorded on the street to the barbiturates.

Availability

Methaqualone does not currently appear to be as easily available on the illicit drug market in Canada as it is in the United States and several other areas of the world.

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[6] The tingling sensation produced by high doses of methaqualone also seems to contribute to a general experience of increased libido.

Methyl Alcohol

(Methanol)

DRUG CLASS: POISON

SYNOPSIS

Methyl alcohol is used chiefly as an industrial solvent and as an adulterant to render undrinkable certain products that contain nonbeverage ethyl alcohol. In the human body, methyl alcohol is changed to formaldehyde and formic acid, which can cause blindness, nerve damage, and severe chemical imbalances associated with the accumulation of acidic materials (acidosis). Ingestion of methyl alcohol in sufficient quantity or prolonged exposure to its vapors can cause coma, possibly followed by convulsions and death from respiratory arrest. Desperate skid-row alcoholics have occasionally consumed methyl alcohol deliberately.

DRUG SOURCE

Methyl alcohol is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Methyl alcohol has no medical use.

STREET NAMES

None in common use.

COMBINATION PRODUCTS

Specifically denatured alcohols,[1] paint removers, cleaning solvents (for use in the restoration of paintings and printmaking and in industry), antifreeze solutions, liquid fuels, Sterno.

[1] SDAG nos. 1-A and 1-E under regulations of the Canadian Excise Act.

PHYSICAL APPEARANCE

Methyl alcohol is a clear, colorless volatile liquid.

DOSAGE

Medical

No medical use.

Nonmedical

As little as a teaspoonful (0.4 cl/0.14 oz) can produce toxic effects.

ROUTES OF ADMINISTRATION

Methanol is consumed orally, and in most cases users are in ignorance of its toxicity.

Persons working with methanol-containing products such as shellacs in improperly ventilated areas may inhale a sufficient quantity to cause medical problems.

EFFECTS OF SHORT-TERM USE

Methyl alcohol is a less potent inebriant than ethyl alcohol; therefore, unless large quantities are consumed or unless ethyl alcohol is consumed simultaneously, inebriation may not be an obvious effect. However, a state of impairment characterized by mild euphoria, loss of inhibitions, and muscular incoordination may be noted shortly after ingestion.

Methyl alcohol acts as a poison in three ways:

1. Methyl alcohol itself causes some depression of the central nervous system similar to but less marked than that caused by ethyl alcohol.
2. Methyl alcohol is metabolized in the body to formic acid and other acids which give rise to a state of acidosis.[2]
3. One of the products of metabolism of methyl alcohol (probably

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[2] A state of reduced alkali reserve in the blood and other body fluids.

formaldehyde) has a directly toxic effect on the retinal cells of the eye.[3]

Since the major toxicity of this substance is attributable to the products of metabolism, symptoms of methyl alcohol poisoning may not be apparent for a period of several hours or possibly for more than a day after its ingestion. Symptoms of methyl alcohol poisoning include:

CNS, behavioral, subjective: blurred vision and other visual disturbances, which may proceed to partial or total blindness; dizziness, restlessness, and vertigo.

Cardiovascular: headache; weak and rapid pulse; cold and clammy extremities; cyanosis.

Respiratory: rapid and shallow breathing.

Gastrointestinal: severe abdominal pain, nausea and vomiting, and sometimes diarrhea.

Other: severe acidosis; severe back pain; impaired kidney function.

Life-threatening overdose can result in severe agitation and delirium, convulsions (occasionally), coma, very slow and labored breathing, and very slow pulse.

When methyl alcohol and ethyl alcohol are ingested simultaneously, the metabolism of methyl alcohol is slowed down so that the toxic metabolites do not accumulate so rapidly. Therefore, the extent of the damage from methyl alcohol ingestion may be reduced, or the onset of toxic effects delayed or on occasion even averted.

EFFECTS OF LONG-TERM USE

Visual impairment or blindness may result from repeated ingestion of even very small quantities of methyl alcohol, or from regular exposure to its vapors in an enclosed atmosphere.

LETHALITY

Death can occur after ingestion of less than 3 cl (1 oz), and 7–10 cl

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[3] As little as 1.5 cl (0.5 oz) of methyl alcohol can cause blindness.

(2.4–3.4 oz) is usually fatal.[4] Death can be sudden or it may follow a coma lasting for several hours; it is almost invariably preceded by blindness (i.e., lack of pupillary response to light). Terminal symptoms include gasping, spasms, and convulsions; death usually results from respiratory arrest. Methyl alcohol has been purposely ingested in both successful and unsuccessful suicide attempts.

The prognosis can be favorable if treatment is rapidly instituted before vision is impaired. With early detection, effective treatment is possible; it includes hemodialysis and the administration of alkalai and ethyl alcohol.

TOLERANCE AND DEPENDENCE

Methyl alcohol is so toxic to the body that a pattern of sustained use, such as would provide a basis for development of tolerance and dependence, is not possible.

PATTERNS OF USE

Occasionally, desperate skid-row alcoholics and persons attempting suicide deliberately consume methyl alcohol. In most cases, as for example with young children, ingestion is inadvertent.

ABUSE POTENTIAL

Because of its toxicity, methyl alcohol has little or no abuse potential.

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[4] Very small doses of methyl alcohol can be lethal to small children. Hence it is essential to store methyl alcohol products out of their reach.

Methylphenidate

DRUG CLASS: CNS STIMULANT;
AMPHETAMINE-LIKE DRUG

SYNOPSIS

While chemically related to the amphetamines, methylphenidate is less potent in terms of its stimulant effects on the central nervous system. For this reason, it is preferable to other stimulants in the treatment of hyperkinesis in children, its primary medical use. At higher doses methylphenidate and the amphetamines produce similar effects. Methylphenidate shares with other central nervous system stimulants the potential for abuse, and both tolerance and dependence have been documented. Because of increased abuse, it has been reclassified in Canada as a controlled drug and is thus less easily available.

DRUG SOURCE

Produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Methidate, Ritalin.

STREET NAMES

None in common use; however, most stimulant drugs are referred to on the street as "uppers."

COMBINATION PRODUCTS

None in use.

MEDICAL USES

- hyperkinesis in children, which is a syndrome characterized by abnormally high levels of usually dysfunctional and nondirected activity, impulsiveness, distractability, and low frustration tolerance;

- mild depression in adults;
- narcolepsy in adults;
- apathetic and withdrawn senile behavior.

One manufacturer is currently proposing its use in injectable form for treating sedative/hypnotic overdose and in accelerating recovery from anesthesia.

PHYSICAL APPEARANCE

Occurs as a white odorless fine crystalline powder that is freely soluble in water and soluble in alcohol.

DOSAGE

Medical

- for hyperkinesis—beginning with 5 to 10 mg orally three times per day (increased as needed, but not to exceed 60 mg daily);
- for mild depression or narcolepsy in adults—40 mg orally per day in divided doses initially, with adjustment as needed;
- for suggested treatment of sedative/hypnotic overdose emergencies—20–30 mg by injection, repeated every 30 minutes as indicated;
- for suggested acceleration of recovery from postoperative anesthesia—10–30 mg by injection.

Nonmedical

There have been reports of heavily dependent abusers taking several hundred milligrams per day. Abusers increase daily dose as tolerance to desired effects develops.

ROUTES OF ADMINISTRATION

Orally or by injection (the latter being the preferred route of abusers).

EFFECTS OF SHORT-TERM USE: LOW DOSES[1]

Methylphenidate produces both desired and adverse effects similar to but less intense than those of amphetamines in comparable doses.

CNS, behavioral, subjective: nervousness; insomnia; suppression of appetite; heightened alertness or drowsiness; euphoria; postponement of fatigue; impairment of voluntary movement; dizziness.

Cardiovascular: headache and rapid and/or irregular heartbeat.

Gastrointestinal: nausea and vomiting.

Other: skin rash.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[2]

Intensification of the low-dose effects may occur, as well as any of the following:

CNS, behavioral, subjective: exhilaration, excitation, agitation; muscle twitching; confusion; hallucinations, paranoid thinking; pupillary dilation.

Cardiovascular: high fever, sweating, flushing, and increased blood pressure and pulse rate.

Gastrointestinal: dryness of the mouth and other mucous membranes; vomiting.

Hazardous dose levels may result in delirium and possibly convulsions, which may be followed by coma.

EFFECTS OF LONG-TERM USE

The principal favorable effects for hyperkinetic children are reported to be decreased hyperactivity, decreased impulsiveness, in-

[1] Single doses within the therapeutic range, up to 60 mg per day in nontolerant persons.

[2] Doses above the medically recommended level in nontolerant users, or lower doses in particularly sensitive individuals.

creased attention span, and more directed and controlled motor activity. The principal unwanted effects which may occur are weight loss, abdominal pain, insomnia, and growth inhibition.

For adults, high doses taken daily by injection may result in a toxic state clinically identical to amphetamine psychosis, a disorder resembling acute paranoid schizophrenia. Cessation of use usually leads to a clearing of the syndrome.

When the injected solution has been prepared from methylphenidate hydrochloride tablets, characteristic lesions have been reported to occur at the sites of injection and in peripheral capillaries. It has been suggested that the lesions may be attributable to the filler present in the tablets.

Other effects of chronic abuse are similar to those produced by amphetamines. (See Amphetamines article above.)

LETHALITY

Severe overdose can lead to convulsions and coma. However, death from methylphenidate overdose has not been reported in the clinical/scientific literature.

TOLERANCE AND DEPENDENCE

Hyperkinetic children do not appear to develop tolerance to the therapeutic effects of methylphenidate (nor to those of amphetamines).

Tolerance to those desired effects sought by the abuser does develop, and physical dependence can result from chronic heavy use. Withdrawal symptoms such as exhaustion and severe emotional depression have been observed. Psychological dependence may also occur. It is characterized as compulsive use of the drug, preoccupation with it, and a craving for its psychological effects which may be so intense that serious distress or feelings of panic may ensue if it becomes temporarily unavailable.

PATTERNS OF USE

At this time, methylphenidate is more widely employed than amphetamines in the treatment of hyperkinesis because it is generally as effective and produces fewer and milder adverse effects. Nowadays methylphenidate is used much less frequently than the tricyclic antidepressant drugs in the treatment of mild depressive disorders.

Past abuse of methylphenidate for its CNS-stimulant properties has led to more rigorous prescribing and distribution controls in Canada. Stiff penalties may be imposed upon those convicted of possession for the purpose of trafficking and for actual trafficking. Increased popularity of methylphenidate among drug abusers appears to be related to a decline in the availability and quality of street amphetamines.

ABUSE POTENTIAL

Dependence Liability

While the dependence liability of methylphenidate is high, it is not as high as that of cocaine, amphetamine, or methamphetamine. When injected, methylphenidate can produce intense euphoria and CNS stimulation; however, these effects are reported to be less powerful than those produced by the other drugs mentioned. Therefore, it is not ordinarily the drug of preference for most stimulant abusers.

Inherent Harmfulness

When administered in low to moderate doses, the adverse effects produced by methylphenidate are usually mild. However, some experienced abusers administer methylphenidate intravenously in very high doses; they are generally aware of the heightened risks and are also willing to accept them.

Methylphenidate is currently legally marketed both in solution for injection and in tablets for oral administration. Street users cannot normally obtain the injectable form and therefore make their own injectable solution from the tablets. The tablets, however, contain certain fillers which may only partially dissolve, and the result is pain and skin lesions at injection sites.

Availability

Reclassification of methylphenidate to its current legal status as a controlled drug has greatly reduced its previous widespread abuse.

Morphine

DRUG CLASS: NARCOTIC ANALGESIC;
OPIATE

SYNOPSIS

Morphine is a naturally occurring substance in the opium poppy, *Papaver somniferum.* It is a potent narcotic analgesic, and its primary clinical use is in the management of moderately severe and severe pain. After heroin, morphine has the greatest dependence liability of the narcotic analgesics in common use. Morphine is administered by several routes (injected, smoked, sniffed, or swallowed); but when injected, particularly intravenously, morphine can produce intense euphoria and a general state of well-being and relaxation. Regular use can result in the rapid development of tolerance to these effects. Profound physical and psychological dependence can also rapidly develop, and withdrawal sickness upon abrupt cessation of morphine use is very similar to that occurring upon cessation of heroin use; many of the symptoms resemble those produced by a case of moderately severe flu.

Morphine is infrequently encountered in the North American street drug culture. However, mainly because of its availability in hospitals, there have been several documented cases of morphine dependence among health professionals.

DRUG SOURCE

Morphine is isolated from crude opium, which is a resinous preparation of the opium poppy, *Papaver somniferum.*

TRADE NAMES

None.

STREET NAMES

“M,” morph, Miss Emma.

DRUG COMBINATIONS

Use of morphine plus cocaine, as well as of morphine plus methamphetamine, has been reported. However, such combinations are not frequently encountered.

MEDICAL USES

- symptomatic relief of moderately severe to severe pain;
- relief of certain types of difficult or labored breathing;
- suppression of severe cough (rarely);
- suppression of severe diarrhea (e.g., that produced by cholera).

PHYSICAL APPEARANCE

Morphine is legally available only in the form of its water-soluble salts. Most common are morphine sulfate and morphine hydrochloride. Both are fine white crystalline powders, bitter to the taste. Both are soluble in water and slightly soluble in alcohol.

DOSAGE

Medical

For moderate to severe pain the optimal intramuscular dosage is considered to be 10 mg per 70 kg body weight (approx. 155 lb) every four hours. However, the typical dose range is from 5 to 20 mg every four hours, depending on the severity of pain. The oral dose range is between 8 and 20 mg; but with oral administration morphine has substantially less analgesic potency (approximately one-tenth of the effect produced by subcutaneous injection) because it is rapidly destroyed as it passes through the liver immediately after absorption. The intravenous route is employed primarily for severe postoperative pain or in an emergency; in this case the dose range is between 4 and 10 mg, and the analgesic effect ensues almost immediately.

ANALGESIC COMPARISONS

Comparison of doses of certain other (subcutaneously injected) narcotic analgesic drugs required to produce approximately the same analgesic effects as 10 mg of morphine (Jaffe & Martin, 1975, p. 256).

	mg	*Trade Name*
Oxymorphone	1.0–1.5	Numorphan
Hydromorphone	1.5	Dilaudid
Heroin	3	–
Metopon	3.5	Metopon
Methadone	7.5–10	–
Oxycodone	10–15	Percodan
Anileridine	25–30	Leritine
Meperidine	80–100	Demerol
Codeine	120	–

Nonmedical

Irregular or intermittent users (who are not substituting the drug for another narcotic analgesic) may start with and continue to use doses within the therapeutic range (i.e., up to 20 mg). However, regular users who employ morphine for its subjectively pleasurable effects frequently increase the dose as tolerance develops. To take several hundred milligrams per day is common, and there are reliable reports of up to four or five grams (4,000–5,000 mg) per day.

ROUTES OF ADMINISTRATION

Morphine may be taken orally in tablet form, and can also be injected subcutaneously, intramuscularly, or intravenously; the last is the route preferred by those who are dependent on morphine.

EFFECTS OF SHORT-TERM USE: LOW DOSES[1]

CNS, behavioral, subjective: suppression of the sensation of and emotional response to pain; euphoria; drowsiness, lethargy, relaxation; difficulty in concentrating; decreased physical activity in some users and increased physical activity in others; mild anxiety or fear; pupillary constriction, blurred vision, impaired night vision; suppression of cough reflex.

Cardiovascular: slight drop in body temperature; sweating.

Respiratory: slightly reduced respiratory rate.

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[1] Single doses of 5–10 mg administered by subcutaneous or intramuscular injection in nontolerant users, to a maximum of 40 mg in divided doses per day.

Gastrointestinal: nausea and vomiting; constipation; loss of appetite; decreased gastric motility.

Other: reduced libido; prickly or tingling sensation on the skin (particularly after intravenous injection).

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[2]

Intensification of the low-dose effects may occur. Duration of effects increases with increased dosage. As the dose increases, (1) sensitivity and emotional response to painful stimuli decrease; (2) there is a greater probability of sleep; (3) ability to concentrate is increasingly impaired; (4) breathing becomes progressively slower and more shallow; and (5) heart rate gradually slows and blood pressure decreases.

The effect most desired by abusers, referred to as a "rush," occurs almost immediately following intravenous injection. The experience is very similar to that reported for heroin at equivalent doses, although somewhat less intense. Users subjectively describe the experience as akin to an intense orgasmic sensation in the abdomen.

In very high doses (i.e., overdose), morphine can produce deep sleep possibly progressing to stupor or coma, low blood pressure, slow and irregular heart rate, cyanosis, shallow and markedly reduced rate of breathing, low body temperature, flaccidity of skeletal muscles, cold and clammy skin, pinpoint pupils, and sometimes pulmonary edema (rapid filling of the lungs with fluids).

EFFECTS OF LONG-TERM USE

Whenever morphine has been provided to morphine-dependent patients in maintenance programs, there has been no indication of marked physiological deterioration or significant psychological impairment. Adverse consequences directly related to long-term morphine use include mood instability,[3] pupillary constriction (which impairs night vision), constipation, reduced libido, menstrual irregularity, and certain types of respiratory impairment.

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[2] Single doses in excess of the therapeutic range (higher than 20 mg) administered by subcutaneous or intramuscular injection in nontolerant users, or lower doses in particularly sensitive individuals.

[3] Mood instability is due to the relatively short duration of action of morphine and most other narcotic analgesics; under controlled conditions the main effects of 10 mg of morphine are reported to last for approximately four to six hours.

LETHALITY

Lethal overdose is characterized by profound coma, pinpoint pupils, cyanosis, and severely depressed respiration; death usually results from respiratory arrest. Lethal overdose by injection in nontolerant persons is estimated to be between 120 and 250 mg; however, high-dose tolerant users have been known to survive 20 times that amount. Acute withdrawal reaction has resulted in death, although rarely.

TOLERANCE AND DEPENDENCE

Tolerance

Marked tolerance to many of morphine's main effects can rapidly develop with regular (i.e., daily) heavy use,[4] particularly if the user administers the drug by intravenous injection.[5] Increasingly greater doses are required to produce desired euphoric, analgesic, and sedative effects. Tolerance to morphine's respiratory-depressant and nausea-producing effects also develops; however, tolerance to its pupillary-constricting effect has not been demonstrated, and tolerance develops only slightly to its constipating effect.

With protracted heavy use, and compensatory increases in daily dose to maintain the desired effects, the user reaches a dose plateau where no amount of the drug can produce the desired intensity of effects. At this point morphine is administered with the same frequency (possibly as often as every six to eight hours) but without additional increases in dose. A user's primary purpose in continued administration of the drug is now to avert withdrawal sickness, which characteristically commences within less than 12 hours after the last dose.[6]

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[4] Tolerance does not develop with infrequent or occasional use.

[5] Early experiments, under medical supervision, employing inpatients with a history of narcotic analgesic dependence indicate that substantial tolerance develops as rapidly as within 7 to 10 days (Martin & Fraser, 1961).

[6] Sensitivity to the desired effects of morphine can be restored after a period of abstinence from it, as well as from other narcotic analgesics (there being a high degree of cross-tolerance among these drugs).

Physical Dependence/Withdrawal

Powerful physical dependence also occurs rapidly in the regular high-dose user. Withdrawal sickness is virtually identical to that described in depth for heroin (see article above), and therefore the stages will only be summarized here.[7]

Early symptoms of withdrawal sickness include watering eyes, nasal discharge, uncontrollable yawning, and heavy sweating. This stage is characteristically followed by an agitated sleep, referred to as a "yen." Agitation upon awakening is accompanied by loss of appetite, depression, dilated pupils, and tremor. At peak intensity (approximately 36–72 hours after cessation of use) symptoms include alternations between chills and flushing, insomnia, continued loss of appetite, violent yawning and sneezing, "gooseflesh," vomiting, nausea, abdominal cramps, elevated heart rate and blood pressure, pains in the bones, muscles, and joints, muscle spasms, and uncontrolled kicking movements.

The severity of the syndrome gradually declines, and most observable symptoms are no longer present within 7 to 10 days after the onset of withdrawal sickness.

Psychological Dependence

The profound impact of dependence on morphine-like drugs is often observable for protracted periods of time after the classical phase of withdrawal sickness has been completed. Chronic depression, anxiety, insomnia, loss of appetite, periods of agitation, and continued craving for the drug can persist for a very long time even among those who may be participating in a methadone program. Such symptoms are often reported to be indicative of psychological dependence. However, a purely psychological explanation may be an oversimplification; much is yet to be understood about the possibly complex physiological adjustments which may result from narcotic analgesic dependence and the fate of these adjustments after withdrawal.

PATTERNS OF USE

During the period between the American Civil War and the early decades of the 20th century, morphine abuse was widespread.[8] Since then heroin has largely replaced morphine as the drug of choice among street drug abusers who prefer to inject narcotic analgesics intravenously.

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[7] The duration of morphine withdrawal sickness is slightly longer than for heroin.

In the past, when morphine was more freely available, it was prescribed by physicians not only for its analgesic properties but also for the many conditions for which tranquillizers are now prescribed. It was even recommended by some physicians as a recreational substitute for alcohol.

Today heroin-dependent users may attempt to obtain morphine illegally when their drug of choice is unavailable, because morphine in sufficient quantities can rapidly and completely suppress heroin withdrawal sickness. Furthermore, because of its availability in medical settings, physicians, nurses, and other health workers have been known to use morphine illegally; however, the few studies concerning narcotic analgesic dependence among medical personnel report a higher rate of meperidine (Demerol) abuse.

Morphine has continued to retain its clinical value as a potent analgesic, and in hospital settings (along with meperidine) it is among the most commonly used drugs in its class for relief of severe pain.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of morphine exceeds that of all other narcotic analgesics in common use except heroin. This reflects both its powerful euphoric and analgesic properties.

Inherent Harmfulness

In low to moderate doses, morphine does not usually produce hazardous effects. However, nausea and vomiting are common, and when they occur the user must be willing to continue to use morphine until tolerance to the unpleasant effects is developed.

Availability

Because morphine may be prescribed for chronically painful conditions, there is a risk to patients of iatrogenic[9] physical dependence. However, the great majority of physicians employ morphine with caution, ordinarily reserving its extended use for patients suffering from severe pain and in many cases for those who are also terminally ill. For most other clinical indications, morphine is prescribed for relatively brief periods. Very strict regulations controlling production and distribution of morphine in Canada and in most other countries greatly reduce its potential for abuse.

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[8] In fact, so many wounded Civil War soldiers developed physical dependence on morphine that the condition was commonly referred to as the "soldier's disease."

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Martin, W.R., and Fraser, H.F., A comparative study of physiological and subjective effects of heroin and morphine administered intravenously in postaddicts, *Journal of Pharmacology and Experimental Therapeutics*, 133: 388-399, 1961.

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[9] I.e., accidentally or unavoidably produced by a course of medical treatment.

Naloxone

DRUG CLASS: NARCOTIC ANTAGONIST

SYNOPSIS

Naloxone is an almost pure narcotic antagonist. If administered to someone who has taken any of the narcotic analgesics, it effectively returns the person to a drug-free state, and can rapidly reverse respiratory depression and other overdose effects. On the other hand, if administered to a person who is in a drug-free state, it exerts little or no pharmacological action. Naloxone and other less complete antagonists[1] are among the few antidotes which can successfully counteract the effects of hazardous overdose across an entire class of psychoactive drugs.

Naloxone induces withdrawal sickness when administered to a narcotic-analgesic-dependent user. For this reason some methadone maintenance programs employ it to verify physical dependence, a precondition of acceptance of the applicant.

There is no evidence that extended use of naloxone can cause harmful physical or psychological effects or dependence. Tolerance to its antagonist actions does not appear to occur.

DRUG SOURCE

Naloxone is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Narcan; Narcan Neonatal.

STREET NAMES

None in common use.

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[1] E.g., nalorphine and levallorphan.

MEDICAL USES

Naloxone can rapidly reverse respiratory-depressant and other overdose effects produced by narcotic analgesics. In this respect, naloxone has various medical uses:

- to counteract the effects of narcotic analgesics on newborn infants when these drugs have been administered to mothers during labor;
- to counteract the effects of narcotic analgesics on postoperative patients when these drugs have been employed during surgery;
- to control seizures sometimes produced by overdose of such narcotic analgesics as meperidine or propoxyphene.

Naloxone is also employed in diagnosing acute narcotic analgesic overdose.

USE OF NALOXONE FOR DIAGNOSIS OF NARCOTIC ANALGESIC OVERDOSE

Respiratory depression is a principal feature not only of narcotic analgesic overdose but also of overdose of other substances such as sedative/hypnotics. Therefore, a quick and accurate diagnosis is essential to the commencement of appropriate treatment, particularly if a patient is stuporous or comatose and cannot provide information. Because naloxone exerts no direct respiratory-depressant action, it can be safely administered to a patient whose breathing is shallow and irregular and markedly slow. If the patient quickly responds favorably to naloxone (i.e., breathing becomes deeper and more rapid), a differential diagnosis of narcotic analgesic overdose can be applied. Respiratory depression caused by overdose of sedative/hypnotics or other substances is not affected by naloxone in standard therapeutic doses. However, less complete narcotic antagonists can further exacerbate depressed respiration produced by sedative/hypnotics.

Naloxone precipitates withdrawal sickness in narcotic-analgesic-dependent users. Therefore, administration of this drug permits the verification of dependence.[2] This method of confirmation is primarily employed in drug-maintenance (such as methadone maintenance) programs so as to screen out drug-seeking rather than drug-dependent individuals.

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[2] When it becomes clear that naloxone is inducing withdrawal sickness, the physician or nurse in charge can then reverse the condition by administration of a suitable amount of a potent narcotic analgesic. Severe withdrawal can usually be completely suppressed by 15 mg of morphine.

Naloxone can reverse the narcotic analgesic (agonist) effects of partial narcotic agonist/antagonist drugs such as pentazocine.

Oral preparations combining methadone and naloxone are sometimes used in methadone maintenance programs so as to prevent patients or others from injecting the methadone. Naloxone exerts little or no pharmacological activity when taken orally, because it is metabolized very rapidly to inactive breakdown products as it passes through the liver immediately after absorption. However, if the patient attempts to inject this drug combination, the naloxone can completely block the desired effects of methadone and precipitate mild withdrawal symptoms.

PHYSICAL APPEARANCE

Naloxone is a slightly off-white, odorless crystalline substance soluble in water and slightly soluble in alcohol.

DOSAGE

Medical

- for adults—between 0.1 and 0.8 mg;
- for newborn infants and children—between 0.005 and 0.1 mg per kilogram body weight.

Nonmedical

This drug is not subject to abuse.

ROUTES OF ADMINISTRATION

Usually by intravenous, intramuscular, or subcutaneous injection. In methadone maintenance programs, oral preparations combine naloxone with methadone.

EFFECTS OF SHORT-TERM USE: LOW DOSES[3]

Reversal of narcotic analgesic overdose effects can occur in as little as one to two minutes.

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[3] Up to 1 mg by injection.

After administration of naloxone, withdrawal sickness in a narcotic-analgesic-dependent patient also occurs within one to two minutes. Usually, the severity of naloxone-induced withdrawal sickness for any given narcotic analgesic is greater than that associated with abrupt termination of use.[4] The reaction is severe because with naloxone the narcotic analgesic blocking effect is immediate; in normal withdrawal the body would have at least some time to compensate for the absence of the drug.

With respect to the above, an "overshoot" phenomenon commonly occurs when naloxone is administered in cases involving either overdose or dependence. For example, not only is depressed respiratory rate after an overdose reversed by naloxone, but for a while breathing may actually become more rapid than before the overdose. The phenomenon may be due to an agonist-induced withdrawal effect (i.e., rebound) or to the antagonism by naloxone of naturally occurring opiate-like substances in the body, known as endorphins.

In the absence of narcotic analgesics in the body, administration of naloxone results in little or no pharmacological activity. However, if a narcotic analgesic is administered a short time after naloxone has been taken, the effects of the narcotic analgesic on the nontolerant person will be blocked either partially or totally (depending on the size of dose of each). For example, 1 mg of naloxone has been demonstrated to completely block the effects of 25 mg of heroin. This effect would be useful in the treatment of addicts who had undergone withdrawal if, say, a single daily dose of naloxone could be taken as a protective drug; unfortunately, however, naloxone's effects are too brief for this approach to be practicable. Recent research has attempted to find longer-acting versions of naloxone. Naltrexone is one such experimental blocker/antagonist.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[5]

1. There have been rare instances of nausea and vomiting in

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[4] Naloxone-induced withdrawal sickness can last for as long as two hours provided no palliative measures are taken (i.e., no narcotic analgesics are administered). In addition to the size of the dose of naloxone, other factors which influence the duration, severity, and type of withdrawal symptoms include the particular narcotic analgesic on which the user is dependent, typical daily dose, chronicity of dependence, general state of health, and concurrent dependence on other drugs.

[5] Doses above the medically recommended level, administered by injection.

postoperative patients when doses higher than therapeutically recommended have been inadvertently employed.

2. Under research conditions, subcutaneously injected doses of 24 mg have occasionally produced drowsiness. Oral doses of 1 gram (1,000 mg) have produced no significant discernible effects.
3. There have been no reported instances of naloxone overdose.

EFFECTS OF LONG-TERM USE

Long-term use does not appear to produce any harmful consequences.

LETHALITY

There have been no reported deaths attributed to naloxone overdose.

TOLERANCE AND DEPENDENCE

Even after protracted administration, such as in the above-noted methadone combinations, tolerance to the narcotic analgesic blocking action of naloxone does not develop, and the ability of naloxone to prevent physical dependence on narcotic analgesics is not diminished.

PATTERNS OF USE

Naloxone is used only under medical supervision and is virtually never knowingly taken by street drug users.

ABUSE POTENTIAL

Naloxone does not produce dependence and has no potential for abuse.

Nicotine

DRUG CLASS: CNS STIMULANT

SYNOPSIS

Nicotine is a mild stimulant which produces small increases in heart rate, blood pressure, respiration, and motor activity. Tobacco, the only natural source of nicotine, was introduced into Europe in the 15th century by Columbus. Since that time, nicotine has become one of the most widely used drugs. The term "nicotine" itself is derived from the surname of a 16-century French diplomat, Jean Nicot, who extolled as virtues the qualities and effects of tobacco smoking.

Nicotine is a stimulant with no medical or therapeutic use. In spite of the state of mild stimulation it produces, many chronic users report a subjectively relaxing experience while smoking.

When tobacco is smoked regularly, the nicotine and such other constituents of inhaled tobacco as tar and carbon monoxide chiefly affect the cardiovascular and bronchopulmonary systems. In the past the tobacco industry argued that the higher incidence of certain serious diseases among chronic smokers—most notably lung cancer—had not been demonstrated to be related directly to smoking. Nowadays the connection is generally acknowledged, and therefore chronic inhalation of tobacco smoke is recognized by experts to be among the greatest of public health hazards.

In spite of an overall decline in the number of cigarette smokers during the past decade, those who do smoke today actually consume an average of 20% more cigarettes than smokers 10 years ago. Regular smoking among young women and those in the middle to late teenage years has also substantially increased during the same time period.

DRUG SOURCE

Nicotine is isolated from the tobacco plants *Nicotiana tabacum*, *Nicotiana rustica*, and *Nicotiana persica*. Nicotine occurs naturally only in tobacco plants. The leaves of the three varieties contain between 0.6% and 0.9% nicotine.

TRADE NAME

Nicorette, recently marketed in Canada by Dow Pharmaceuticals, is a gum containing 2 or 4 mg of nicotine resin; it is recommended for use by smokers who are attempting to quit or cut down. It is the only medical product containing nicotine.

STREET NAMES

There are numerous current and past colloquial terms for tobacco, which mainly refer to cigarettes. One of particular interest which has recently gained prominence is "cancer stick."

DRUG COMBINATIONS

Street drug users sometimes combine tobacco with other drugs such as cannabis or phencyclidine (PCP) and smoke the combination. Heroin was often cheap and easily available to American soldiers in Vietnam, some of whom smoked a combination of heroin and tobacco.

MEDICAL USES

The only medical products containing nicotine are chewing gums such as Nicorette, which are designed to help the smoker quit or cut down the habit. Lobeline, a milder alkaloid than nicotine, is marketed as Nikoban and is used essentially for the same purpose.

PHYSICAL APPEARANCE

Pure nicotine is an oily liquid varying in color from clear to brown; nicotine sulfate and other nicotine salts are white or colorless crystals in their pure form. Smoking tobacco is a brown shredded plant-leaf material. Chewing tobacco is a dark, moist compressed mass of plant-leaf material. Snuff is a powdered plant material.

Nicotine sulfate preparations for use as pesticides include concentrated solutions (e.g., Black Leaf 40) and powders impregnated with the drug.

DOSAGE

Medical

The producers of Nicorette recommend chewing 10 pieces of gum per day, and in exceptional cases up to 20 pieces. Nicorette is marketed in two strengths; one piece of gum contains either 2 or 4 mg of nicotine resin complex.

Nonmedical

A typical cigarette contains approximately 15–20 mg of nicotine; however, when it is normally smoked, less than 1 mg reaches the bloodstream. For Canadian brands of cigarettes, smokers will take between 0.09 and 1.34 mg into their bloodstream per cigarette. Tar yields per cigarette, which correlate very highly with nicotine content, vary between 1.2 and 23.4 mg per cigarette. Different cigarettes also produce between 1.7 and 39.1 mg of carbon monoxide, a gas which also contributes to debilitating lung diseases when chronically inhaled.

The actual amount of these substances reaching the bloodstream, within these wide ranges, is determined by the following factors: (1) the type of tobacco; (2) whether or not there is a filter; (3) the type and effectiveness of the filter; (4) the number of puffs per cigarette and depth of inhalation; (5) the proportion of the cigarette smoked prior to its being extinguished; and (6) the manner in which the cigarette is smoked.[1]

A smoker who uses one pack of 20 cigarettes per day of Canadian cigarettes will take into his bloodstream between 1.8 and 26.8 mg of nicotine, between 24 and 428 mg of tar, and between 34 and 789 mg of carbon monoxide. The amount of each depends on the factors noted above.

ROUTES OF ADMINISTRATION

Nicotine is ingested by smoking, by chewing, or by sniffing tobacco as snuff. Cigarettes have been eaten by children, sometimes with lethal results.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

For the nonsmoker, as little as one or two puffs may result in flushing, nausea, gagging, vomiting, coughing, sweating, abdominal

[1] For example, with low-tar/low-nicotine cigarettes, if smokers cover the small air holes in the filter with their fingers, the nicotine yield increases.

[2] One or two cigarettes.

cramps, weakness, watering eyes, dizziness, and diarrhea. In smokers, the following may occur:

CNS, behavioral, subjective: Electroencephalogram (EEG) waves are similar to those produced in a mild state of physiological arousal, although chronic smokers often report relaxation (possibly in part due to relaxation of the voluntary muscles).

Cardiovascular: increased heart rate, blood pressure, and cardiac output, and in some users abnormally rapid heart rate; reduced cutaneous blood flow in the limbs; slight drop in skin temperature.

Respiratory: increased respiratory rate; irritation of the mucosal lung and upper respiratory tissue; increased bronchial secretion, which is then followed by inhibition of such secretion.

Gastrointestinal: increase in the rate of basal metabolism; temporary reduction of hunger; increased salivary secretion, which is then followed by inhibition of such secretion; inhibition of gastric secretion; inhibition of urinary output; increased motor and tone activity of the bowel, and occasionally diarrhea.

Other: increase in production of adrenaline.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES

Intensification of the low-dose effects for smokers may occur; however, for some smokers certain low-dose effects occur only after the consumption of higher daily doses.

EFFECTS OF LONG-TERM USE

Smoker's Respiratory Syndrome

With regular heavy smoking the following syndrome often occurs: labored breathing, shortness of breath, wheezing, constriction of the pharynx, and frequent upper respiratory infections. The syndrome clears when smoking is discontinued. (See Volle & Koelle, 1975.)

Respiratory Diseases

In comparison to nonsmokers, chronic smokers are at greater risk of developing:

- pneumonia;
- lung complications after surgery, e.g., infections, blood clots (and of dying from these causes);
- chronic bronchitis (cigarette smoking is its principal cause);
- emphysema, a condition in which the lungs lose their elasticity and retain too much air;
- lung cancer.

Cigarette smoking is the main cause of lung cancer in men. It is also a cause of lung cancer in women but accounts for a smaller proportion of cases, probably because fewer women were smoking 20–30 years ago.[3] Risk of developing lung cancer increases with the number of cigarettes smoked per day, number of years one has smoked, and earliness of the age at which one started. However, if smoking is discontinued and if no irreversible disease has started, the lungs gradually clear themselves. Studies have shown that the average ex-smoker who has not smoked cigarettes for 10 years has about the same health prognosis and life expectancy as one who has never smoked.

Cardiovascular Disease

The cardiovascular system may also be severely affected by chronic smoking; smoking can act jointly with other factors (such as high blood pressure, physical inactivity, high serum cholesterol, hereditary predisposition) to increase the risk in smokers of developing:

- coronary heart disease;
- peripheral blood vessel disease, a condition involving the narrowing or blockage of blood vessels in the arms and legs;
- death from brain blood vessel disease.

Other Harmful Effects

Chronic smokers are also more likely to develop cancer in other parts of the body—for example, the larynx, mouth, and esophagus. In addition, an association is suggested between cigarette smoking and cancer of the bladder, kidney, and pancreas.

Male cigarette smokers are more likely to get stomach ulcers than nonsmokers; they also have higher death rates from this condition. In addition, cigarette use slows the healing of stomach ulcers and increases the danger of complications.

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[3] The prevalence of lung cancer in women is now increasing in proportion to the increased number of women smokers.

Women who smoke during pregnancy tend to have smaller babies and are more likely to give birth prematurely. They also have a greater number of stillbirths, and death among their newborn babies is more common. Infants living in homes of smokers are more prone to respiratory infections.

Chronic smokers can suffer appetite loss, impairment of the senses of taste and smell, and diminished physical endurance; they consistently perform more poorly on some fine motor tasks (because of "nicotine tremor") than nonsmokers.

LETHALITY

Although nicotine and other constituents of tobacco are harmful to health and have been shown to be linked to numerous potentially lethal diseases, death directly attributable to nicotine in tobacco form has rarely been recorded, except in the case of infants and young children who have eaten cigarettes or cigarette butts and ashes. Fortunately, gastric absorption of swallowed nicotine in tobacco is sufficiently poor that the minute amount required to produce vomiting usually has its effect before lethal quantities can be absorbed.

A lethal dose in adults is estimated to be approximately 60 mg; however, very small amounts (as low as 4 mg) are reported to have produced severe illness. Pure nicotine is one of the most lethal substances known to man. A few drops of the pure substance on the tongue would quickly kill a healthy adult. Nicotine is a common ingredient in insecticides.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance to nicotine does develop and is most clearly reflected in the many short-term symptoms which are either not present or greatly reduced while the chronic user is smoking. However, it appears that tolerance to these effects does not develop uniformly; as well, there are substantial individual differences in the pace with which users increase their daily nicotine intake.

Psychological and Physical Dependence/Withdrawal

It is generally agreed that psychological dependence on nicotine develops among chronic smokers of several cigarettes per day; however, the issue regarding the occurrence of physical dependence has not been resolved. Although many researchers believe that nicotine produces physical dependence, a highly consistent withdrawal syndrome has not been fully established, and there is considerable variation in the type and intensity of observed withdrawal effects after chronic smoking has been terminated. Some of the more frequently observed symptoms are depression, anxiety, restlessness, irritability, sleep disturbances, difficulties in concentration, constipation, sweating, and a drop in blood pressure and pulse rate.

In the chronic user, psychological dependence is amply demonstrated in that the need for the psychological effects of smoking is so central to the person's thoughts, emotions, and activities that it is difficult for the person to discontinue the habit. Temporary unavailability of cigarettes or having to remain in a setting where smoking is prohibited (e.g., on public transit, in a theatre, in a supermarket) for a sustained period is likely to produce a strong craving for a "smoke" and mild to moderate distress. Many heavy smokers are clearly relieved to leave such settings and often immediately light up. As well, although the complex factors pertaining to the phenomenon are not yet understood, regular smokers insist that smoking often produces a relaxing or calming effect and claim that to be one of the primary reasons for continuing to smoke. Long after chronic smokers have quit, many report that stressful situations frequently produce a craving for smoking.

PATTERNS OF USE

Tobacco use is now almost universally viewed as a major cause of ill health. In Canada, the current annual cost of tobacco-related disability exceeds $1.5 billion; however, a comparable amount is collected in taxes on tobacco sales. About $3.1 billion is spent in Canada each year on tobacco products, close to $475 for each of the 6.5 million smokers. Canadians have the highest per capita tobacco consumption in the world. Nearly all of Canada's tobacco is grown in Ontario, where it is the most important cash crop, accounting for more than 25% of the province's total crop value. More than 95% of the crop is made into cigarettes.

Smokers comprise about 42% of Canadians over the age of 14. The proportion is considerably higher in Quebec and slightly lower in the other provinces. The great majority smoke cigarettes.

Overall, the proportion of smokers is declining, largely because adult men are giving up the habit, although recent increases in the number of women smokers also seem to have slowed. While relatively fewer people are smoking now than 10 years ago, those who do smoke are smoking about 20% more cigarettes than in 1970. Average consumption by smokers is above 20 cigarettes per day.

While the causes of smoking are determined by many factors, it is certain that teenagers are more likely to smoke if their parents, other family members, and/or friends do. Approximately 40% of the 15-to-19 age group smoke regularly, an increase of nearly 25% in the last decade. However, the average daily consumption among teenagers tends to be considerably lower than among smokers in other age groups.

Smokers tend to use other drug substances more heavily than nonsmokers, especially alcohol, caffeine, or both.

ABUSE POTENTIAL

In comparison to other drugs which produce physical dependence, the degree of that produced by nicotine is slight, but the severity of psychological dependence increases with chronicity and frequency (i.e., the daily number of cigarettes smoked). However, while the dependence liability of nicotine is moderate and recovery after withdrawal is common, (1) the immediate gratification produced by the first puff, (2) the generally long delay in the onset of harmful physical consequences after the onset of heavy regular smoking, and (3) the easy availability of tobacco result in high abuse potential.

REFERENCE

Volle, R.L., and Koelle, G.B., Ganglionic stimulating and blocking agents, in *The Pharmacological Basis of Therapeutics*, L.S. Goodman and A. Gilman (Eds.), 565-574, Macmillan, New York, 1975.

Oxycodone

DRUG CLASS: NARCOTIC ANALGESIC;
OPIATE

SYNOPSIS

Oxycodone is a semisynthetic narcotic analgesic derived from chemical manipulation of codeine. It produces potent euphoric, analgesic, and sedative effects and has a dependence liability similar to that of morphine. Its main clinical use is in the management of moderate to severe pain. One of the principal pharmacological advantages of oxycodone is that, unlike many other powerful narcotic analgesics, it retains substantial potency when administered orally. For this reason it is widely used in the treatment of outpatients, and for the same reason has recently become a popular drug of abuse. Chronic high-dose abuse of oxycodone can produce powerful physical dependence, and withdrawal sickness upon abrupt termination of use is similar to that produced upon termination of morphine. When clinically used for extended periods at even low doses, it can produce mild physical dependence. Tolerance to its euphoric, analgesic, and sedative effects can develop rapidly, particularly when it is abused at high dose levels.

Oxycodone has a very high abuse potential not only because it is highly effective when taken orally but also because (1) it is relatively easily available when compared to most other powerful narcotic analgesics; (2) it is inexpensive; and (3) it has a relatively high degree of consistent purity.

DRUG SOURCE

Oxycodone is produced by the pharmaceutical industry through chemical modification of codeine.

TRADE NAME

Supeudol.

STREET NAME

Percs.

COMBINATION PRODUCTS

- Percodan (oxycodone, ASA, and caffeine);
- Percocet (oxycodone and acetaminophen);
- Percobarb (oxycodone and hexobarbital).

MEDICAL USES

For moderate to severe pain (and, in addition, for control of fever and inflammation in the combination drug Percodan).

PHYSICAL APPEARANCE

Oxycodone occurs as a white odorless crystalline powder that is slightly soluble in water and soluble in alcohol. Its salts are freely soluble in water and only slightly soluble in alcohol.

DOSAGE

Medical

- Percodan—for moderate pain, 2.25 mg up to four times per day; for moderately severe pain, 4.5 mg up to four times per day;
- Percocet—as for Percodan;
- Supuedol—10 or 20 mg suppository up to three times per day.

Nonmedical

Daily doses of up to 100 mg or more have been reported. Dosage progressively increases as tolerance develops to the desired effects.

ROUTES OF ADMINISTRATION

Orally[1] or by suppository. Dependent users have been reported to inject the drug occasionally.

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[1] One of the principal advantages of this drug is that it retains at least 50% of its analgesic potency when administered orally; it is five to six times more potent than an equal dose (by weight) of codeine taken orally.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, behavioral, subjective: suppression of the sensation of and emotional response to pain; euphoria, relaxation, sedation; lightheadedness, dizziness; drowsiness; mild clouding of mental function; in some people mild depression and anxiety; pupillary constriction (which can impair night vision) and blurred vision.

Cardiovascular: sweating.

Respiratory: slight reduction in respiratory rate.

Gastrointestinal: nausea and vomiting, loss of appetite, and constipation.

Other: reduced libido; itching.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

Intensification of low-dose effects may occur. The duration of effects increases with the size of the dose and (1) sensitivity and emotional response to painful stimuli decrease; (2) there is a greater probability of sleep; (3) ability to concentrate is increasingly impaired; (4) breathing becomes progressively slower and more shallow; and (5) there is a gradually slowing heart rate and mildly decreased blood pressure.

In very high doses (i.e., overdose) oxycodone can produce deep sleep which may progress to stupor or coma; low blood pressure; slow heart rate; cyanosis; shallow breathing and markedly reduced rate of breathing; reduced body temperature; flaccidity of skeletal muscles; and cold and clammy skin.

EFFECTS OF LONG-TERM USE

There have been no indications of marked physiological deterioration or significant psychological impairment among long-term oxycodone abusers. Those adverse effects which can be directly attributed to chronic abuse of this drug include mood instability,[4] pupillary constriction, impaired night vision, blurred vision, constipation, menstrual irregularity, and certain types of respiratory impairment.

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[2] Single doses within the therapeutic range administered orally to nontolerant users, up to approximately 20 mg/day.

[3] Single doses in excess of the therapeutic range administered orally in nontolerant users, or lower doses in particularly sensitive individuals.

LETHALITY

Severe overdose may result in respiratory arrest, circulatory collapse, cardiac arrest, and death. The estimated lethal dose for a nontolerant adult is approximately 500 mg. Overdose of the combination products produces additional effects:

1. Ingestion of large quantities of Percodan may further result in acute salicylate poisoning; each compound tablet (both the oxycodone 4.5 mg and oxycodone 2.25 mg) contains ASA 325 mg.
2. Ingestion of large quantities of Percocet may further result in acute acetaminophen poisoning; each compound tablet (both the oxycodone 4.5 mg and oxycodone 2.25 mg) contains acetaminophen 325 mg.
3. Ingestion of large quantities of Percobarb may further result in acute barbiturate poisoning; each compound capsule (oxycodone 4.5 mg) contains hexobarbital 100 mg.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance to many of the main effects produced by oxycodone can develop rapidly with regular use; these include the euphoric, analgesic, sedative, respiratory-depressant, and nausea-producing actions. Tolerance does not appear to develop to oxycodone's pupillary constricting effect, and it only partially develops to the constipating effect.

As tolerance develops to the desired effects, the daily dose must be increased in order to compensate for decreased sensitivity. After several such increases, the user may reach a dose plateau where no further increase in the size of the dose is capable of producing the intensity of effects desired. If users do not then switch to a more potent narcotic analgesic, it is very likely that they will self-administer the drug with the same frequency and dose, but now primarily to prevent the onset of withdrawal sickness.

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[4] This is due to the relatively short duration of the effects of oxycodone, i.e., four to five hours.

Physical Dependence/Withdrawal

Powerful physical dependence on oxycodone can result for the regular heavy user; and abrupt abstinence results in a withdrawal sickness as severe in type and intensity as that produced upon abstinence from morphine.[5] Early symptoms may be present approximately eight hours after the last dose and include watering eyes, nasal discharge, uncontrollable yawning, and heavy sweating, often followed by agitated sleep. At peak intensity (approximately 36–72 hours after cessation of use), the above are intensified and, additionally, there is severe agitation; alternations between chills and flushing; tremors; severe yawning and sneezing; loss of appetite; insomnia; "gooseflesh"; vomiting, nausea; abdominal cramps; elevated heart rate and blood pressure; pains in the muscles and joints; muscle spasms and uncontrolled kicking movements.

Intensity of the syndrome gradually declines, and most observable symptoms are no longer present within approximately seven days after onset.

Psychological Dependence

The profound impact of dependence on such narcotic analgesic drugs as oxycodone is often observable for long periods of time after the classical phase of withdrawal sickness is completed. Chronic depression, anxiety, insomnia, loss of appetite, periods of agitation, and continued craving for the drug can persist for months (or in some cases even years). Such symptoms are often reported to be indicative of psychological dependence. However, a psychological explanation may be an oversimplification; much is yet to be understood about the possibly complex adjustments which may result from narcotic analgesic dependence and the fate of these adjustments after withdrawal.

PATTERNS OF USE

Oxycodone has now been in clinical use for several decades; as was the case with many other narcotic analgesics, it was initially hoped to be a safe alternative to morphine. In fact, when each is taken orally in comparable doses, oxycodone has much greater analgesic potency. For this reason, it has become an increasingly attractive drug in the management of moderate to severe pain among outpatients.[6] Furthermore, because it can produce a potent euphoric effect, oxycodone has also rapidly become an important drug of abuse. Street abusers obtain oxycodone by theft or robbery from pharmacies, by forging prescriptions on stolen prescription blanks, and by faking painful conditions which are difficult for a physician to confirm objectively (e.g., back pain). It is not unusual for an oxycodone abuser to obtain several prescriptions per week from different doctors. Oxycodone is also sold on the illicit drug market.

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[5] At any time during withdrawal sickness, administration of a suitable dose of oxycodone (or of many other narcotic analgesics) can either partially or completely suppress the syndrome.

ABUSE POTENTIAL

Dependence Liability

Currently available oxycodone preparations contain fillers which make injection both difficult and painful. Therefore, it is generally taken orally by abusers; under this condition, the euphoric effect, although still powerful, is experienced less rapidly than that of other powerful narcotic analgesics administered by injection, and is less intense than if it were administered by injection.

However, oxycodone hydrochloride in pure form is soluble and can be injected in large quantities directly into the bloodstream. Under these conditions, both the immediacy and potency of its effects are approximately equal to what would result from injection of a similar dose (by weight) of morphine. Thus, its inherent dependence liability is as great as that of morphine.

Inherent Harmfulness

In low to moderate doses, oxycodone usually does not produce hazardous effects. However, nausea and vomiting are common early side effects, and the user must be willing to continue taking the drug regularly in order to acquire tolerance to these effects.

Availability

Because oxycodone is frequently prescribed for chronically painful conditions, there is a risk of patients developing iatrogenic (medically induced) physical dependence. Some physicians mistakenly believe that the risk of physical dependence on oxycodone is greatly reduced because it is administered orally; therefore, they tend to prescribe oxycodone less prudently than they would prescribe other powerful narcotic analgesics. However, chronic use of oxycodone, even if administered orally at low doses, can still produce physical dependence.

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[6] The estimated per capita quantity of oxycodone used in Canada for medical and scientific purposes has more than trebled during the 1970s.

The main issues related to the current popularity of oxycodone among narcotic analgesic abusers appear to be (1) its relatively easy availability; (2) compared to street-purchased narcotic analgesics its relatively low cost; and (3) again unlike street narcotic analgesics, its high degree of relatively consistent purity. For these reasons, regular abusers of oxycodone are willing to forgo the more immediate and intense effects of injected narcotic analgesics.

PCP

(Phencyclidine)

DRUG CLASS: DISSOCIATIVE ANESTHETIC

SYNOPSIS

Phencyclidine is a dissociative anesthetic originally employed in human anesthesia but later limited to veterinary medicine because of certain highly undesirable side effects. Some of these very side effects, however, are what make PCP so attractive to the street drug user. It possesses both stimulant and depressant properties. It can produce hallucinations, relaxation, feelings of dissociation from the environment, and sometimes intense euphoria. Furthermore, it can induce a spectrum of perceptual and cognitive changes which are similar to those produced by LSD. Users commonly experience distortions in their perceptions of time, space, and body image, as well as visual and auditory distortions.

PCP can also produce very severe traumatic psychic effects at low doses, even in those who have had previous favorable experiences with it. It is not uncommon for users to report agitation, disorganization of thinking, and intense feelings of alienation accompanied by paranoia while under its influence. This last experience has sometimes provoked violent and bizarre behavior. Large doses can produce convulsions and respiratory arrest.

DRUG SOURCE

Phencyclidine is produced through chemical synthesis by the veterinary pharmaceutical industry and by illicit laboratories.

TRADE NAMES

No products are legally prepared for human use.

STREET NAMES

There are many; a few of the more widely used include angel dust, crystal, hog, peace pill, horse tranquillizer.

DRUG COMBINATIONS

PCP is sometimes taken with LSD. It is also sprinkled on marijuana and smoked.

MEDICAL USES

None. PCP was used by veterinarians to anesthetize and tranquillize large animals.

PHYSICAL APPEARANCE

Although phencyclidine occurs as a white crystalline powder which rapidly dissolves in water or alcohol, PCP is encountered on the street in various colors in the form of pills, capsules, or powder. It is quite often misrepresented to the street buyer as methamphetamine ("speed"), mescaline, LSD, or other psychoactive substances such as THC (tetrahydrocannabinol, the active ingredient in cannabis).

DOSAGE

Medical

Phencyclidine is no longer used in clinical medicine. When used by veterinarians, the dose varied in proportion to the type of animal and the purpose for which it was used (tranquillization or anesthesia).

Nonmedical

The typical dose is 5–10 mg. There have been reports that chronic users may take single doses in the form of "joints"—the drug sprinkled on a leaf substance such as parsley and smoked—of up to 80–100 mg two to three times per day continuously over a period of a few days. There have been unsubstantiated reports of 0.5–1.0 gram (500–1,000 mg) consumed in 24 hours.

ROUTES OF ADMINISTRATION

PCP may be taken orally in the form of a liquid, tablet, or capsule; "snorted" (sniffed); smoked sprinkled on marijuana, parsley, tobacco, mint, or other smokable substance; or injected (usually intravenously).

EFFECTS OF SHORT-TERM USE: LOW DOSES[1]

CNS, behavioral, subjective: There is a fairly wide variation among users in possible perceptual, cognitive, and emotional experiences produced by PCP. In addition to the size of the dose, drug effects are influenced by the setting, the user's expectations,[2] past drug experiences, and personality; it is not unusual for the user to experience differing reactions to PCP during different drug-taking episodes.

Effects can include:

- mild to intense euphoria;
- relaxation and sedation or pleasant stimulation;
- feelings of dissociation from the environment and of unreality;
- distortion of body image, often manifested as sensations of weightlessness and floating;
- distortion of time (minutes may appear to pass as slowly as hours);
- distortion of space;
- visual and auditory distortions (true hallucinations can occur but are much more likely to be experienced at higher doses) and possibly distortions involving any of the other senses;
- difficulties in concentrating, thinking, or maintaining attention.

Primarily physical effects can include speech disturbances such as difficulty in articulating, motor incoordination, impairment of fine dexterity, pupillary constriction, blurred vision, and sometimes dizziness and/or drowsiness.

Adverse effects can range between mild and severe. Any of the following symptoms may occur: anxiety (quite common), agitation, paranoid thinking, panic, or even terror; confusion and thought disorganization; precipitation of previously latent psychosis; blank staring, stupor, and catatonic rigidity; mutism (inability to speak); intense feelings of alienation; depression sometimes sufficiently severe to precipitate a suicide attempt; hostile and possibly violent and bizarre behavior; amnesia for events occurring during the drug-taking episode; a painful reaction to sounds.

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[1] 5 mg or less, taken orally by nontolerant users.

[2] The user's subjective expectations are particularly important in the case of PCP because this drug is so frequently misrepresented to be other substances. Severe agitation or panic may ensue for the unsuspecting user who is anticipating the very different effects of another drug.

At moderately higher doses (e.g., 10 mg), the anesthetic and analgesic properties of PCP are likely to be manifested. Sensitivity to pain decreases, and probability of sleep increases. There may be a psychic experience similar to sensory isolation.

Cardiovascular: increased blood pressure and heart rate; perspiration; nausea and vomiting.

Respiratory: increased breathing rate but with breathing tending to be more shallow.

Other: increased urinary output.

The effects of relatively pure PCP when smoked are perceptible within a few minutes, peaking in approximately 30 minutes. The "high" lasts between four and six hours, with a gradual decline of effects ("coming down") usually completed within 24 hours.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[3]

Intensification of low-dose effects may occur, as well as any of the following effects:

CNS, behavioral, subjective:[4] erratic and bizarre behavior and compulsive repetitive movements; severe psychological disorganization and acute toxic psychosis, often manifested in a clinical picture of confusion, incoherent speech, disorientation, paranoia, possibly violent or assaultive behavior, agitation and restlessness, autism, preoccupation or obsession with what would otherwise be trivial matters, hallucinations, and grandiose delusions. States of panic, terror, and overwhelming fear of imminent death have been observed. This state frequently lasts for a period of several days.

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[3] Doses in excess of 10 mg in nontolerant users, and lower doses in particularly sensitive individuals.

[4] As with low doses, perceptual, cognitive, and emotional experiences may vary considerably among users.

Other physical effects can include involuntary rapid movement of the eyeballs; muscular rigidity; decreased awareness of the sensations of pain, touch, and position; absence of or decreased gag and corneal reflexes; posture spasms in which the head and heels are bent backward and the body bowed forwards; stupor or coma.

Cardiovascular: irregular heartbeat. Abnormally high blood pressure may alternate with abnormally low blood pressure. Elevated body temperature and heavy sweating may alternate with chills and shivering.

Respiratory: slow, shallow, and irregular breathing.

Gastrointestinal: severe nausea and vomiting and persistent heavy salivation.

Other: decreased urinary output.

At very high doses (i.e., severe overdose) coma, convulsions, and death (usually attributed to respiratory arrest) can occur.

EFFECTS OF LONG-TERM USE

What is known about the effects of chronic use of PCP is based largely on case reports of clinicians and investigators. Although some of these reports appear to do no more than present users' perceptions at second hand, the symptoms described by regular users are consistent.

Like methamphetamine ("speed") users, chronic PCP users often engage in "runs"—repeated administrations of the drug for a period of two to three uninterrupted days without sleeping and with little or no eating. The "run" is followed by a protracted period of sleep from which the user often awakens feeling disoriented and depressed. "Runs" may be repeated as frequently as two to four times per month.

Chronic high-dose users report impairment of thinking and memory, particularly recent memory; this impairment may persist for several months after cessation of use. As well, some users report unpleasant “flashbacks” similar to those experienced by LSD users. Persistent speech problems (including stuttering, the inability to articulate, and the inability to speak at all) have been observed; these also may continue for extended periods after the use of PCP has been terminated. Chronic and possibly severe anxiety and depression are common; indeed, some regular users become sufficiently depressed to attempt suicide.

Although early experiences with PCP usually occur in the company of others, there is often gradual social withdrawal and isolation. Many users report divorce, lost employment, and disrupted education. Since most regular users of PCP also smoke marijuana and may use other drugs, these other substances may contribute to the above spectrum of symptoms.

PCP-influenced behavior is frequently unpredictable and sometimes extremely violent. Toxic psychosis, similar to amphetamine psychosis or acute schizophrenia, has been observed in some chronic users who had no known psychiatric disturbances prior to their regular use of PCP. The syndrome is manifested in aggressive or assaultive behavior, paranoia, delusional thinking, and (mainly auditory) hallucinations.

Most chronic users acknowledge having experienced at least one “bad trip,” but in most cases it did not result in their terminating use of PCP. Apparently the possibility of the extraordinary “high” and feelings of euphoria are sufficiently powerful to encourage further use. Psychological dependence does seem to develop for many high-dose users and is explored below (see Tolerance and Dependence).

LETHALITY

Deaths from acute overdose of PCP have occurred with amounts estimated to be between 150 and 200 mg.[5] While the usual clinical picture is coma, convulsions, and respiratory arrest, the following have also been reported to result from extremely high doses of PCP: repeated uninterrupted convulsions, acute hypertensive crisis, hemorrhage of the blood vessels of the brain, and kidney failure. Overdose may also be complicated by the simultaneous presence of other drugs in the body.

[5] It is likely that lower doses could prove fatal to some.

High doses of CNS-depressant drugs (e.g., sedative/hypnotics or narcotics) substantially increase the risk of respiratory arrest.

Many PCP-related deaths have also resulted from the psychological impact of the drug. For example, depression of sensory and muscular control has led to several accidental drownings. (It is not unusual for PCP users to attempt to swim in an effort to enhance the sensations of weightlessness and of floating.) Other deaths have resulted from leaps from high places and vehicle accidents. Successful suicides, homicides (sometimes bizarre), self-mutilations, and other results of extremely violent behavior have also been reported to be associated with the often unpredictable effects of this drug.

TOLERANCE AND DEPENDENCE

Tolerance to the effects of PCP has yet to be clearly demonstrated. However, preliminary observations and subjective reports suggest that it can develop with protracted use.

Two separate investigations of chronic users of PCP, in widely separated geographic areas, have resulted in similar findings (Fauman & Fauman, 1978; Lerner & Burns, 1978). Initially only a few puffs (a few milligrams) of a PCP "joint" were required to produce the euphoric "high." Most of the subjects indicated a consistent need to increase their intake in order to maintain the "high," and within two to six weeks many were smoking one to two "joints" at a time. (It was estimated that each "joint" contained between 50 and 80 mg of PCP.) Some users reported taking even higher doses at one sitting. Although their reports were unsubstantiated, some also claimed to use up to one gram (1,000 mg) within a 24-hour period.

Reports of physical dependence in humans are rare, and none is objectively confirmed. However, withdrawal symptoms upon abrupt termination of use have been reported for some animal species.[6] Psychological dependence has been reported in several chronic users in the form of a craving for the effects of PCP when it was temporarily unavailable.

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[6] Experiments designed to study withdrawal symptoms in humans have not been performed. Such experiments were necessary, for example, to establish that humans could become physically dependent on cannabis.

PATTERNS OF USE

Phencyclidine was initially introduced into clinical medicine as an anesthetic in the 1950s. Disturbing reports regarding convulsions during surgery and such postoperative effects as agitation, confusion, disorientation, and hallucinations quickly led to its being completely discontinued for human use. It was again marketed in the 1960s exclusively as an animal anesthetic under the trade name Sernylan. It also appeared on the streets of San Francisco at the same time and was referred to in the drug subculture as "PeaCe Pill" (hence PCP). However, some scientists use PCP as an abbreviation for its chemical name, phenylcyclohexylpiperidine. Because of the variety of its psychoactive properties, it has been sold on the street not only as PCP but also as a host of other desired substances, most commonly THC, methamphetamine, mescaline, and LSD. Large profits have been made by such misrepresentation, particularly in areas where the desired drugs are scarce and expensive, for the chemicals needed for the synthesis of PCP cost very little.

It is difficult to estimate the number of persons who have used PCP. Although caution should be exercised in interpreting the statistics, the number of PCP-related deaths and of hospital emergency department admissions due to PCP overdose consistently increased during the 1970s. A trend toward increased incidence of PCP abuse seems to be continuing in spite of the substantial negative publicity the drug has received in the past few years.

ABUSE POTENTIAL

Dependence Liability

Physical dependence on PCP has not yet been demonstrated, and the incidence of psychological dependence is not known. However, intense euphoria appears to be one common reaction to PCP and accounts at least in part for its appeal to those who use it regularly.

Inherent Harmfulness

The effects of PCP vary considerably among users and from one drug episode to another; it is not possible to predict with any certainty what a given user's reaction will be to this drug on any given occasion. Even in low doses PCP can produce very harmful psychological effects, and at higher doses the effects may be life-threatening.

The drug is currently broadly abused. No doubt abuse would be even more widespread if it were not for the dangers attendant on its use, the unpredictability of these dangers, and its consequent reputation in the street-drug subculture.

Availability

PCP is currently widely available on the illicit North American drug market.

REFERENCES

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Pentazocine

DRUG CLASS: NARCOTIC AGONIST/ANTAGONIST

SYNOPSIS

Pentazocine was synthesized as part of a continuing effort to find a drug sufficiently potent to provide relief from moderately severe to severe pain without the danger of abuse associated with narcotic analgesics. In fact, while it has analgesic properties, it is also a weak narcotic antagonist; that is to say, it can precipitate mild withdrawal symptoms when administered to narcotic-analgesic-dependent users.[1]

When taken orally, pentazocine has an analgesic potency greater than meperidine (e.g., Demerol); when administered by injection its analgesic potency is approximately one-third that of morphine.

Recently pentazocine has surfaced as a drug of abuse in its own right because it can produce typical narcotic analgesic euphoria as well as pleasant sensations of floating. Some abusers have likened its effects to those produced by marijuana. At high doses pentazocine can produce toxic psychosis. Furthermore, chronic injection of pentazocine can result in significant tissue damage at injection sites.

Studies have revealed that pentazocine dependence may result from chronic use at relatively low dose levels (e.g., 180 mg per day and over). Distinctly unpleasant withdrawal symptoms following chronic use include abdominal cramps, anxiety, restlessness, pallor, exaggerated breathing, nausea and vomiting, chills, elevated body temperature, sweating, and watering eyes.

A recently developed form of abuse of this drug involves the intravenous administration of a liquid mixture of crushed pentazocine tablets and certain antihistamine tablets. In particular, pentazocine has been combined with tripelennamine; the combination is referred to as "Ts and Blues."[2] Users report a euphoric heroin-like effect immediately

[1] See Narcotic Analgesics chapter in section 2 for discussion of agonists/antagonists.

[2] Tripelennamine is an antihistamine marketed under the trade name Pyribenzamine. The origins of this combination are not known; however, among street abusers of pentazocine in certain areas of North America it appears to be quite common.

after injection. An associated hazard is that undissolved particles of the binding substances in tripelennamine tablets can block small blood vessels and thus damage lung tissue when this mixture is injected intravenously over a protracted period of time.

DRUG SOURCE

Pentazocine is produced through chemical synthesis by the pharmaceutical industry.

TRADE NAME

Talwin.

STREET NAMES

None specifically for pentazocine.

COMBINATION PRODUCTS

Medical

Talwin Compound–25 and Talwin Compound–50 (both contain pentazocine, ASA, and caffeine).

Nonmedical

"Ts and Blues" (pentazocine and tripelennamine).

MEDICAL USES

Relief from moderate to severe pain.

PHYSICAL APPEARANCE

Pentazocine hydrochloride occurs as a white crystalline powder, soluble in water and in alcohol.

DOSAGE

Medical

Orally—50–100 mg every three to four hours; by injection—30 mg three times per day.

Nonmedical

Doses substantially in excess of 1 gram (1,000 mg) per day have been reported in tolerant users.

ROUTES OF ADMINISTRATION

Orally by tablet, rectally by suppository, and by subcutaneous, intramuscular, and intravenous injection. Abusers sometimes crush the tablets and prepare them in solution for injection.

EFFECTS OF SHORT-TERM USE: LOW DOSES[3]

CNS, behavioral, subjective: relief from and reduced emotional response to moderate to severe pain;[4] euphoria in some and anxiety in others; sedation; lightheadedness, dizziness; blurred vision. Some report sensations of floating. Infrequently occurring are hallucinations, confusion, nightmares, excitement, and tremors. Because pentazocine is also a weak narcotic antagonist, it may produce mild withdrawal symptoms if administered to a person dependent on a narcotic analgesic.

Cardiovascular: headache; sweating.

Respiratory: slight respiratory depression.

Gastrointestinal: nausea and vomiting; constipation.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[5]

Intensification of the low-dose effects may occur, as well as any of the following effects:

1. Sensitivity and emotional response to painful stimuli decrease.

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[3] Single doses within the therapeutic range administered orally or by injection to nontolerant persons. Symptoms tend to be similar to many of those produced by narcotic analgesics.

[4] Approximate analgesic potency of pentazocine: orally, 50 mg pentazocine is equivalent to 100 mg meperidine (e.g., Demerol); by injection, 30 mg pentazocine is equivalent to 10 mg morphine.

[5] Single doses in excess of the therapeutic range (or lower doses in particularly sensitive individuals) administered either orally or by injection to nontolerant persons.

2. There is a greater probability of sleep, often accompanied by highly vivid dreams.
3. Blood pressure and heart rate increase and may become abnormally high.
4. Respiratory depression can occur but is more moderate than for high doses of narcotic analgesics.
5. Ability to concentrate is increasingly impaired.
6. Toxic psychotic states have occasionally occurred, and are characterized by hallucinations, delusions, disorientation, and confusion.

At very high doses (i.e., overdose) pentazocine can produce deep sleep, possibly progressing to stupor or coma. Blood pressure and heart rate are abnormally high, and heartbeat may be irregular. Seizures may occur.

EFFECTS OF LONG-TERM USE

In one study, normal volunteers received daily doses of 100–800 mg of pentazocine per day for between 35 and 200 days. There were no significant effects on vital signs except for one case. However, there are several clinical reports of pentazocine-induced emotional disturbances among medical patients on high-dose therapy. Most commonly occurring is depression, sometimes quite severe. The above-described acute toxic psychosis persisted in some patients and disappeared only after the use of pentazocine was discontinued. Nightmares, dizziness upon awakening, other sleep disturbances, and concentration difficulties have also occasionally been associated with chronic use of this drug.

Chronic injection of pentazocine results in the following distinctive features at the sites of injection:

- woody fibrotic tissue extending well beyond the sites of injection;
- irregularly shaped ulcers often sufficiently deep to expose the muscle;
- a halo of discoloration around these ulcers;
- a lack of pain despite these tissue damages.

CHRONIC INJECTION OF PENTAZOCINE AND TRIPELENNAMINE

Street users who inject a combination of pentazocine and tripelennamine ("Ts and Blues") report experiencing intense euphoria immediately after intravenous injection; this effect seems to be very similar to the typical heroin-like "rush"—an intense orgasmic sensation in the abdomen. However, it appears that there is a potentially serious health hazard associated with chronic intravenous injection of this combination. In the past few years several people in the Cincinnati area have been admitted to the University Medical Center whose presenting symptoms were shortness of breath and wheezing accompanied by a decrease in arterial blood oxygen. All regularly injected a crude solution containing pulverized pentazocine and tripelennamine tablets that had been designed for oral consumption.

Evidence suggests that these symptoms are likely to have been caused by insoluble particles of talc, the key binding substance in tripelennamine tablets. Intravenous injection of solutions containing such particles has been demonstrated to block small blood vessels and thus cause serious tissue damage to the lungs.

LETHALITY

Death due exclusively to overdose of pentazocine has not been reported.

TOLERANCE AND DEPENDENCE

With regular use, tolerance can develop to both the analgesic and euphoric properties of pentazocine. However, there are insufficient data to make comparisons between it and the narcotic analgesics in terms of the rate at which tolerance develops.

When pentazocine was originally marketed, it was considered a nonaddictive drug with low abuse potential. However, an increasing body of evidence has not supported this early optimism. Indeed, recent studies have revealed that physical dependence can occur even in moderate therapeutic doses (i.e., 180 mg per day and over) when administered daily for a period of at least one month. Premature underestimation of pentazocine's dependence liability has led to accidental dependence among patients using the drug and among physicians themselves. In most cases the dependence has resulted from needle administration, but in a few cases it has resulted from exclusively oral use.

Withdrawal sickness after abrupt termination of chronic high-dose use of pentazocine is not as pronounced as that occurring after termination of most narcotic analgesics. It is, however, sufficiently unpleasant to cause dependent users to strongly resist discontinuing its use. Commonly observed withdrawal symptoms include abdominal cramps, anxiety, chills alternating with elevated temperature, nausea and vomiting, sweating, and watering eyes. Agitation, insomnia, and depression have also been reported.

PATTERNS OF USE

Pentazocine taken by itself does not appear to be popular with street drug users; furthermore, users of narcotic analgesics cannot substitute this drug so as to postpone withdrawal sickness when their preferred drugs are not available. Nonetheless, reliable reports indicate that the combination “Ts and Blues” has recently become quite popular in some large cities in the midwestern and eastern United States. Data regarding experiences in Cincinnati with this combination are cause for concern. The local pharmaceutical association in that city has reported that the most commonly recognized forged prescriptions are for pentazocine and tripelennamine. In addition, in 1977 the Cincinnati Drug and Poison Information Center received as many requests for information about “Ts and Blues” as about heroin.

It is not yet understood why these two drugs combine to produce a highly potent euphoric effect when taken intravenously. Taken alone, tripelennamine appears to produce little or no euphoria. It would therefore seem that the antihistamine potentiates the effects of pentazocine.[6]

There are insufficient data to determine how widely this combination is used among street drug abusers. Another recent report indicates that in Indiana, injection of pentazocine in combination with yet another antihistamine compound, promethazine,[7] has also become popular. Because of the potentially serious complications which may result from intravenous injection of these combinations, incidence of their abuse warrants careful scrutiny.

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[6] Potentiation is a phenomenon that occurs with many drug combinations such that the effect created by their combined actions is greater than one would expect from the simple addition of their separate effects. (See section 1.)

[7] Promethazine is marketed under the trade names Histanil and Phenergan.

ABUSE POTENTIAL

Dependence Liability

When it is taken orally, the dependence liability of pentazocine is probably similar to that of moderately potent narcotic analgesics taken orally, such as meperidine; however, when administered intravenously in combination with the above-noted antihistamines, the intense euphoria that these drugs produce suggests a very high dependence liability for the combination.

Inherent Harmfulness

Chronic administration by intravenous injection, as well as by other injection routes, is greatly restricted by the propensity of pentazocine to produce significant tissue damage at the injection sites. Both high-dose medical use and abuse are further restricted by harmful psychological effects on some users. Seizures have occasionally been precipitated by very high doses of pentazocine.

Availability

In Canada, pentazocine is a controlled drug, widespread abuse has not been noted, and it is infrequently found on the street. However, in some areas of the United States, it appears to be relatively easily available to street drug abusers.

Phenothiazines

DRUG CLASS: MAJOR TRANQUILLIZERS;
ANTIPSYCHOTICS;
ANTIEMETICS[1]

SYNOPSIS

The phenothiazines are commonly called major tranquillizers or antipsychotic agents. These terms relate to the major psychiatric disorders for which they are effective therapeutic agents—namely, acute and chronic psychotic states and severe psychoneurotic states. Violent, severely anxious, and hyperactive patients can be calmed by the phenothiazines without falling into sleep or insensibility.

One of the most important features of these drugs is that they rarely produce physical or psychological dependence even over an extended period of administration. Moreover, even in very large doses they are highly unlikely to induce serious respiratory depression, anesthesia, or coma. Because they can be used with less risk and also produce greater specificity of effects, the phenothiazines have largely replaced the barbiturates (and other less effective drugs) in calming psychotic patients. With the introduction of the phenothiazines it became possible to treat effectively a substantial proportion of psychotic patients on an outpatient basis rather than through prolonged periods of institutional care.

DRUG SOURCE

Phenothiazines are produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

There are almost a dozen phenothiazines currently used in Canada. Examples of some of the more important substances include chlorpromazine (e.g., Largactil), thioridazine (e.g., Mellaril), trifluoperazine (e.g., Stelazine), and perphenazine (e.g., Trilafon).

[1] Antiemetic refers to the capacity to suppress nausea.

STREET NAMES

None.

COMBINATION PRODUCTS

Elavil Plus; Etrafon (perphenazine and amitriptyline).[2]

MEDICAL USES

- acute and chronic functional psychotic symptoms including agitation, excitement, and violent behavior, as well as manic behavior associated with manic/depressive psychosis;
- severe anxiety states accompanying psychoneurotic disorders;
- symptoms of certain types of psychoses of organic origin, including those produced by infection, by metabolic disorders, and by some toxic substances;
- alcoholic hallucinosis;
- organic brain syndrome associated with aging (e.g., senile psychosis and cerebral arteriosclerotic psychosis);
- sometimes, severe nausea and vomiting and intractable hiccup.

PHYSICAL APPEARANCE

Two of the most widely used phenothiazines are chlorpromazine and trifluoperazine. Chlorpromazine occurs as a very bitter odorless white or creamy-white crystalline powder, very soluble in water and alcohol; trifluoperazine occurs as a bitter white to pale yellow crystalline powder, soluble in water and slightly soluble in alcohol.

DOSAGE

Medical

Daily doses of the phenothiazines differ markedly from one drug to another, since these substances range widely in potency. For example, the daily oral dose of chlorpromazine ranges between 30 and 1,000 mg; in unusual cases higher daily doses may be administered. On the other hand, the daily oral dose of trifluoperazine ranges between 4 and 10 mg. Substantially smaller doses can be employed when the phenothiazines are injected, because their effects are more intense with injection.

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[2] Amitriptyline is an antidepressant.

One drug in this family, fluphenazine enanthate (e.g., Mellaril-enanthate), can be administered by injection in a single dose of 25–50 mg once every two weeks, by virtue of the very slow speed at which it is eliminated from the body.

Nonmedical

These drugs are rarely subject to nonmedical use.

ROUTES OF ADMINISTRATION

The phenothiazines can be taken orally by tablet or capsule, or in solution by injection (usually intramuscular), or rectally by suppository.

EFFECTS OF SHORT-TERM USE[3]

The effects produced by phenothiazines vary to some extent from one drug to another, as does the intensity of the effects. Nonetheless, there is substantial overlap from one drug to another with regard to most of the effects.

It is important to note that the full antipsychotic effects of phenothiazines are often not observed until several weeks after the initial administration.

CNS, behavioral, subjective: Normal research subjects, when given therapeutic doses of chlorpromazine, manifest passivity, apathy to the external environment, dramatically reduced emotional responsivity, and drowsiness; however, unlike with barbiturate-induced sedation, these subjects are easily roused and generally do not experience impairment of intellectual functions, although psychomotor performance tends to be impaired.

In patients undergoing treatment the following effects have been observed: marked reduction in agitation and excitement;

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[3] Single doses within the therapeutic range taken orally by nontolerant users—e.g., 50–100 mg of chlorpromazine.

sedation and sometimes oversedation and lethargy; drowsiness; impaired motor functions; increased or decreased motor activity; muscle twitches; muscular rigidity; dizziness; tremors; suppression of cough reflex; blurred vision; pupillary contraction; infrequently, paradoxical excitement and worsening of psychotic symptoms; and occasionally seizures, particularly in those patients with a history of seizures.

Cardiovascular: drop in blood pressure when attempting to rise to a standing position; sometimes, irregular heartbeat; sometimes, abnormal increase or decrease in heart rate; sweating; mild elevation of or drop in body temperature.

Gastrointestinal: dry mouth or excessive salivation; difficulty in swallowing; upset stomach; constipation. Some phenothiazines suppress nausea and vomiting, while others may induce these reactions.

Other: urinary retention.

EFFECTS OF LONG-TERM USE

Severe psychotic symptoms are gradually ameliorated by phenothiazines. The intensity and frequency of hallucinations greatly declines, delusional thinking can be substantially suppressed, and agitation, mania, and bizarre behavior may be completely eliminated. Reality orientation can significantly improve, and psychotic patients are generally more easily managed. In many cases, the continued use of phenothiazines can result in total, or almost total, remission of psychotic symptoms. The overall results for patients can be (1) fewer hospitalizations throughout their lifetime and, in some cases, lifelong maintenance in the community without hospitalization; (2) briefer periods of hospitalization; (3) improved interpersonal and vocational functioning—that is, a more productive lifestyle; and (4) a greater capacity to care for their own needs.

In the past (prior to the introduction of the phenothiazines) most psychotic patients admitted to psychiatric hospitals remained there for most or all of their lives. There are still some chronic, severely psychotic patients maintained on phenothiazines who do not sufficiently improve to be released into the community. Nonetheless, those who require permanent institutional care now represent a very small minority of patients, and even they are now better able to function within the institutional setting.

Adverse Effects

Although the phenothiazines have proven to be highly beneficial to large numbers of psychotic patients, they can also produce a spectrum of undesired side effects. Some patients suffer from slow, awkward, and clumsy movement, muscle tremors, muscle rigidity, and uncontrollable facial masklike grimaces; these symptoms are thought to result from the selective impairment that phenothiazines produce on motor nerve impulse transmission.[4] However, the severity and frequency of the symptoms vary both with the particular phenothiazine used and the size of the daily dose, as well as from one individual to another. Ordinarily the adverse effects are not pronounced with moderate daily therapeutic doses of chlorpromazine.

A syndrome which may also occur with chronic high-dose phenothiazine therapy is called tardive dyskinesia; it is characterized by rhythmic involuntary movements of the jaw, face, tongue, and/or mouth, sometimes accompanied by involuntary movements of the extremities. In some cases, these phenomena are irreversible.

Some patients undergoing phenothiazine therapy may experience a compulsive need to move about constantly and are often so restless that they are unable to sit or remain in one place except for short periods of time. This condition differs from agitated pacing in that the constant compulsive movement does not appear to be under the control of the patient; moreover, the compulsive movement disappears when phenothiazine therapy is discontinued, whereas agitated pacing may continue.

Other neurological complications which can occur with the use of phenothiazines include spasmodic contractions of the neck muscles, lowered seizure threshold, visual difficulties, and impairment of those brain centres that regulate body temperature.

Skin reactions to phenothiazine therapy sometimes occur and can include extreme sensitivity to sunlight (the reaction is similar to severe sunburn) and dermatitis. Some patients continue to experience a sudden drop in blood pressure when they attempt to stand up and so feel faint and dizzy for a short while. Serious blood disorders including jaundice also occasionally occur with chronic phenothiazine use.

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[4] The symptoms can be treated with antiparkinsonism drugs.

LETHALITY

Deaths exclusively due to phenothiazine overdose occur infrequently, and cases of survival after ingestion of such massive acute overdoses as 30 grams (30,000 mg) of chlorpromazine have been reported. Lethal overdose causes severe central nervous system depression. Early drowsiness progresses to coma and is usually accompanied by very low blood pressure, abnormally rapid heartbeat, respiratory depression, and vasomotor collapse. The syndrome may be punctuated by periods of tremor or muscle twitching, muscle spasms, rigidity, and severe seizure activity. Death may result from respiratory failure or from cardiac arrest.

Phenothiazines can potentiate the hazardous effects of other CNS-depressant drugs such as barbiturates, alcohol, and narcotic analgesics; ingestion of such drug combinations has caused a number of fatalities.

TOLERANCE AND DEPENDENCE

Chlorpromazine produces a more intense degree of sedation than do most other commonly used phenothiazines, and in certain cases this is a beneficial effect; however, tolerance develops to the sedative effect with regular use of chlorpromazine or other phenothiazines. In most cases, little or no tolerance develops to the antipsychotic effects, and many patients can be maintained on the same daily dose for years.

Physical dependence on phenothiazines seems to develop in some patients who use these drugs for extended periods of time; a few days after abrupt abstinence, some patients experience a mild withdrawal syndrome characterized by muscular discomfort and sleeping difficulties. A rebound worsening of the pre-drug-therapy psychotic state sometimes occurs, and for a while patients may experience varying degrees of difficulty in performing voluntary motor functions.

PATTERNS OF USE

Phenothiazines are the most widely used drugs in the treatment of severe psychoneurotic disorders and a variety of psychotic states.

Street abuse of these drugs is extremely rare, although there have been isolated incidents involving the combined ingestion of phenothiazines and the other commonly abused CNS depressants, presumably to enhance the sedative effects of the latter. The outcome is usually drowsiness and sleep; however, more severe consequences have occurred. For a while, phenothiazines were fairly widely used in emergency departments of hospitals for treating hallucinogen-induced agitation and psychosis; this practice is now infrequent, for the side effects produced by the phenothiazines often proved more harmful than any beneficial effect. Less potent and potentially less harmful agents, such as diazepam, have proven to be useful in the immediate management of hallucinogenic "bad trips."

ABUSE POTENTIAL

The dependence liability of phenothiazines is extremely low, in fact among the lowest of all psychoactive drugs. These drugs do not produce any lasting effects that might be desired by drug abusers. For example, sedation produced by such agents as chlorpromazine is only temporary with regular use. Other side effects make phenothiazines unattractive to potential abusers.

PMA

(Paramethoxyamphetamine)

DRUG CLASS: HALLUCINOGEN WITH STIMULANT PROPERTIES

SYNOPSIS

PMA (paramethoxyamphetamine) is a synthetic amphetamine derivative with both stimulant and hallucinogenic properties. It has no medical use. PMA has been sold on the street usually as MDA (methylenedioxyamphetamine), and in both its hallucinogenic and stimulant properties it is very similar to MDA. However, PMA is much more potent and far more toxic: in Ontario between March and August 1973, there were nine deaths of young people that were confirmed to be attributable to PMA. The toxicity of PMA is related to excessive central nervous system (CNS) stimulation.

DRUG SOURCE

Produced through chemical synthesis in illicit laboratories.

TRADE NAMES

Not applicable; the drug has no medical use.

STREET NAME

Death drug.

COMBINATION PRODUCTS

None has been encountered in Canada.

MEDICAL USES

None.

PHYSICAL APPEARANCE

In the form of its salts (PMA hydrochloride or PMA sulfate), it is a white crystalline material if pure. In impure forms, it ranges from yellow-white to amber and may be powder, chunks, or gummy material.

Both pure and impure forms have been marketed in capsules or simply wrapped in foil or plastic.

DOSAGE

Medical

Not applicable.

Nonmedical

The effective dose has been estimated at approximately 50–75 mg. Much larger doses have been used, probably by accident, and have been fatal in some instances.

ROUTES OF ADMINISTRATION

PMA may be taken orally, sniffed, or injected.

EFFECTS OF SHORT-TERM USE

Psychoactive effects are similar to those of mescaline. However, the minimum effective dose of PMA is approximately one-fifth that required for mescaline. Adverse effects may include:

CNS, behavioral, subjective: hallucinations; delirium; restlessness, agitation; muscle contractions; hyperactivity (thrashing around); rigidity.

Cardiovascular: rapid heart rate; increased blood pressure; high fever; perspiration.

Gastrointestinal: nausea and vomiting.

Higher doses can produce very high fever, convulsions, coma, and death.

EFFECTS OF LONG-TERM USE

Not known.

LETHALITY

High doses can be fatal. PMA has been sold on the street quite often as MDA, but is more potent; thus the unsuspecting user can easily take an overdose. As noted, PMA use was definitely associated with nine deaths in Ontario during a six-month period in 1973, and it is quite possible that other deaths due to PMA overdose may have occurred but without the association documented.

TOLERANCE AND DEPENDENCE

It is unknown whether tolerance or dependence develops to PMA, as there have been virtually no clinical studies on the effects of PMA on human subjects.

PATTERNS OF USE

In most cases of reported use, PMA was thought to be MDA. Thus a pattern of occasional use is most likely. During the past several years, there have been no reports of street use of PMA. That PMA appeared on the street at all may have been due to the fact that it is more easily synthesized than MDA and other chemically related drugs.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of PMA is not known, but is is likely to be very low; chemically similar drugs such as MDA have a low dependence liability.

Inherent Harmfulness

Since PMA can be lethal even at moderate doses, its reputation discourages all but naive users, a factor which limits its abuse potential.

Availability

There have been no reports of PMA use for several years; in fact, its original synthesis was probably accidental, and its manufacturers unaware of the low threshold of its lethal effects.

Propoxyphene

DRUG CLASS: NARCOTIC ANALGESIC;
OPIOID

SYNOPSIS

Propoxyphene is a wholly synthetic narcotic analgesic. In terms of analgesic and euphoric potency it is among the mildest of all commonly used drugs in this class; propoxyphene's sole medical use is for relief of mild to moderate pain. Although it is much more frequently prescribed than any other narcotic analgesic, the degree to which it is effective in reducing pain has recently been questioned by researchers. Some have reported the analgesic potency of propoxyphene to be approximately one-half that of codeine; others have found the standard oral dose (65 mg) to be no more effective than a standard oral dose of ASA (650 mg), and in small doses to be no more effective than a placebo.

Abusers report that they can achieve a pleasant state of euphoria when propoxyphene is injected intravenously; but chronic needle administration of this drug can cause severe damage to veins and to local tissue at the sites of injection. In very high abusive doses, its principal toxic effects are respiratory depression, psychosis, and seizures. For these reasons, it is rarely the exclusive drug of choice for abusers of narcotic analgesics; rather, because of its easy availability, it is frequently abused in combination with other drugs in order to produce a more pleasurable "high."

When propoxyphene is administered orally in low doses, tolerance to its mild analgesic and euphoric effects develops gradually. However, even when it is taken orally, chronic high-dose abuse can result in physical dependence; withdrawal symptoms after abrupt abstinence tend to be milder than for other narcotic analgesics.

DRUG SOURCE

Produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

- propoxyphene napsylate—Darvon-N;
- propoxyphene hydrochloride—Algodex, Depronal-SA, Novopropoxyn, Pro-65, 642 (also Darvon, which is not available in Canada).

STREET NAMES

None in common use.

COMBINATION PRODUCTS

- Darvon-N with ASA (propoxyphene napsylate and ASA);
- Darvon-N compound (propoxyphene napsylate, ASA, and caffeine);
- 692 (propoxyphene hydrochloride, ASA, and caffeine).

MEDICAL USES

For mild to moderate pain which is not adequately relieved by ASA.

PHYSICAL APPEARANCE

Propoxyphene hydrochloride occurs as a white, bitter crystalline powder freely soluble in water and in alcohol. Propoxyphene napsylate occurs as an odorless, bitter, white crystalline solid which is very slightly soluble in water and soluble in alcohol.

DOSAGE[1]

Medical

For mild to moderate pain—one capsule or tablet either 32–65 mg propoxyphene hydrochloride or 100 mg propoxyphene napsylate three to four times per day.

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[1] Propoxyphene hydrochloride 65 mg has approximately the same analgesic potency as propoxyphene napsylate 100 mg, as both contain the same amount of propoxyphene.

Nonmedical

Daily doses of propoxyphene hydrochloride in excess of 600–800 mg have been commonly reported. In rare instances, some highly tolerant abusers have been known to take as much as 3,000 mg per day.

ROUTES OF ADMINISTRATION

Orally by tablet, by capsule, or in liquid suspension. Preparations specifically for injection are no longer marketed, and currently available oral preparations are difficult to dissolve for needle administration.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

CNS, behavioral, subjective: suppression of the sensation of mild to moderate pain;[3] occasionally mild euphoria or in some cases mild emotional depression, anxiety, or (paradoxically) excitement; dizziness, lightheadedness; sedation, drowsiness, or in some cases insomnia; weakness; pupillary constriction (which can impair night vision) and blurred vision.

Cardiovascular: sweating; headache (infrequently).

Gastrointestinal: nausea, vomiting; abdominal pain; constipation.

Other: itching, skin rash.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[4]

Intensification of the low-dose effects may occur. Duration of effects increases with the size of the dose. Also (1) sensitivity and emotional response to painful stimuli decrease; (2) there is a greater probability of sleep; (3) ability to concentrate is increasingly impaired; (4) breathing becomes progressively slower and more shallow; and (5) there is a gradual slowing of heart rate and mild decrease in blood pressure. In contrast to many other narcotic analgesics, higher doses of propoxyphene can produce CNS excitation manifested as muscle twitches and tremors. When administered to experienced users by intravenous injection, higher doses of propoxyphene can produce a state of moderately intense euphoria and the typical narcotic analgesic "rush." This is described as akin to an intense orgasmic sensation in the abdomen, experienced almost immediately after injection. (However, because of its irritating properties, injection of propoxyphene is quite painful.)

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[2] Single doses within the therapeutic range administered orally to nontolerant persons to a maximum of approximately 250–300 mg propoxyphene hydrochloride per day in divided doses.

[3] The analgesic potency of propoxyphene has recently been a subject of controversy among researchers. Usually, its analgesic potency is reported to be approximately one-half that of codeine; however, some researchers report that two ASA tablets (650 mg) are more effective in relieving pain than 65 mg (the standard dose) of propoxyphene hydrochloride. It has also been reported that 32 mg of propoxyphene hydrochloride is no more effective in relieving pain in some individuals than a placebo.

[4] Single doses in excess of the therapeutic range administered orally to nontolerant persons, or lower doses in particularly sensitive individuals.

At very high doses (i.e., overdose) propoxyphene can produce toxic psychosis in some users, characterized by disorientation, confusion, delusions, and hallucinations. Also occurring are seizures (frequently), disturbance of the acid-base balance in the body, deep sleep possibly progressing to stupor or coma, shallow breathing and markedly reduced rate of breathing, slow heart rate, low blood pressure, and cyanosis.

EFFECTS OF LONG-TERM USE

Chronic injection of propoxyphene is more painful than injection of most other common narcotic analgesics; there is marked tissue irritation and abscesses at the injection site, and severe damage to veins is also common.

Very-high-dose oral abuse is limited by potentially serious side effects. Abusers may experience a persistent toxic psychotic state which disappears only after there has been a drastic reduction in daily dose or after complete abstinence. Marked agitation, tremors, and startle responses (and sometimes seizures) are characteristic of chronic very-high-dose abuse.

LETHALITY

Severe overdose can result in coma, convulsions, circulatory collapse, cardiac arrest, and death from respiratory arrest. The lowest reported dosage associated with death in an adult is 800 mg. In other cases where propoxyphene was considered to be the cause of death, blood levels ranged between 0.1 and 6.0 mg/100 ml. Suicides by way of lethal doses of propoxyphene have also been reported.

Although rarely the drug of choice for experienced narcotic analgesic abusers, propoxyphene is often taken in conjunction with other drugs in order to achieve a more pleasurable "high." Combinations of high doses of propoxyphene and other CNS depressants which also can depress respiration (e.g., alcohol or barbiturates) have been implicated in several deaths, particularly in the past few years.

Large doses of propoxyphene compounds containing ASA may cause acute salicylate poisoning.

TOLERANCE AND DEPENDENCE

Tolerance

Tolerance to the analgesic and mild euphoric effects of propoxyphene occurs with regular use, but appears to develop more gradually than for other narcotic analgesics when they are taken orally. However, tolerance to these effects at very high doses cannot accurately be gauged, for as users approach such dose levels they are obliged to discontinue increasing their typical daily dose because of the very unpleasant and potentially hazardous side effects. There is evidence that when propoxyphene is intravenously administered for a period of a few weeks, tolerance to its effects can develop much more rapidly than when it is orally administered.

Physical Dependence/Withdrawal

Propoxyphene, when chronically abused at doses substantially above the therapeutic range, can produce physical dependence; withdrawal sickness occurs after abrupt cessation of protracted use. Symptoms tend to be similar to those reported for other narcotic analgesics, but typically are much milder. They include tremor, insomnia, agitation, profuse sweating, and elevated blood pressure, pulse, and temperature. As well there can be abdominal and other muscular cramps, hyperactive deep-tendon reflexes, dizziness, "gooseflesh," nausea, and vomiting. Seizures have occasionally been observed.

Administration of sufficient doses of propoxyphene or other narcotic analgesic drugs can completely suppress propoxyphene withdrawal.

Although relatively few in numbers, there have been documented cases of medically induced accidental acquisition of physical dependence on propoxyphene among patients suffering from chronic pain. In one study, none had a history of either psychiatric illness or previous drug abuse;[5] in some cases, the daily dose reached as high as 2 grams (2,000 mg). Upon abrupt cessation of use all patients experienced withdrawal sickness.

Psychological Dependence

Psychological dependence on propoxyphene can occur when it is regularly administered, even at low daily doses under medical supervision. Patients have been known to remain for years on the same small maintenance dose; their use persists even though tolerance to the analgesic effect of their regular daily dose has had ample time to develop and the drug no longer has any inherent pharmacological value. These patients report a persistent craving for the psychological effects of propoxyphene, a preoccupation with securing an ample supply, and psychic distress when they are temporarily unable to obtain the drug. These symptoms can occur in the absence of physical dependence—that is, when a consistent and clearly defined physiological withdrawal syndrome does not appear to occur after abrupt abstinence.

PATTERNS OF USE

Propoxyphene is among the most widely prescribed of the narcotic analgesics; in excess of 35 million prescriptions were written in the United States alone in 1977. Abuse or misuse of the drug at doses above therapeutically indicated levels is probably quite common, for its potentially harmful effects when abused have only recently received public attention. It is likely that many patients who are using propoxyphene are not sufficiently aware of the danger of taking the drug in combination with alcohol and other CNS depressants. A concerted effort on the part of physicians and pharmacists is necessary in order to educate and caution their patients appropriately.

Propoxyphene is used in the drug subculture, but it is not usually the drug of exclusive choice of sophisticated abusers. Because of its low euphoric potency it is usually taken in combination with other drugs.

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[5] In fact, some of these patients had become physically dependent on propoxyphene without experiencing the typical euphoria associated with narcotic analgesics.

Some heroin users acknowledge taking large quantities of the drug in attempting at least partially to suppress withdrawal sickness when other narcotic analgesics are unavailable.

ABUSE POTENTIAL

Dependence Liability

The dependence liability of propoxyphene is among the lowest of the commonly used narcotic analgesics; in fact, it is below that of codeine. Propoxyphene produces relatively mild euphoria when taken orally even at high doses; and while more intense euphoria can occur when high doses are administered intravenously, the adverse effects of its needle administration militate against chronic abuse by this route.

Inherent Harmfulness

In addition to the negative consequences of protracted needle administration, the potentially hazardous effects of very high doses of propoxyphene greatly restrict the upper dose limits of abuse.

Availability

In that it is more easily available than other narcotic analgesics with the exception of codeine,[6] propoxyphene has a relatively high potential for abuse. It is important to note that the intensity of its desired effects can be potentiated (although with considerable risk) by other easily available drugs such as alcohol.

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[6] In Canada and the U.S., while a doctor's prescription is required for all propoxyphene products, some codeine combination products are available without prescription.

Psilocybin

DRUG CLASS: HALLUCINOGEN

SYNOPSIS

Psilocybin and the closely related substance psilocin are hallucinogens found primarily in the *Psilocybe* and *Conocybe* mushrooms, which grow in many parts of the world. Psilocybin has been used ritually in Mexico and Central America for centuries to produce altered states of consciousness similar to those produced by mescaline and LSD. Among the psychoactive effects produced by psilocybin are:

- vivid visual "pseudohallucinations" and distortions, which are known to the user to be unreal;
- synesthesias—the paradoxical melding of the senses such that, for example, sounds seem to be "seen";
- changes in perceptions of time, space, and body image.

In most instances, the above effects are valued by the user and are the reason the drug is normally taken; however, sometimes the user may be frightened or even terrified by these same manifestations (i.e., experience a "bad trip").

Psilocybin is most highly valued for its ability to induce experiences which are subjectively considered to be profoundly revelatory or even mystical.

Tolerance to the effects of psilocybin develops rapidly and the user must periodically discontinue taking it in order to regain original sensitivity.

Physical and psychological dependence are not known to occur.

DRUG SOURCE

Psilocybin is chiefly derived from the mushroom *Psilocybe mexicana* and some other *Psilocybe* and *Conocybe* species (Lewis & Elvin-

Lewis, 1979). The drug can also be chemically synthesized, but only with considerable difficulty and expense. Furthermore, the synthetic product deteriorates rapidly and is difficult to store. For these reasons, chemical synthesis is undertaken infrequently.

TRADE NAMES

Psilocybin is not used for any medical purpose.

STREET NAMES

Magic mushroom; mushroom; shroom.

COMBINATION PRODUCTS

None.

MEDICAL USES

None.

PHYSICAL APPEARANCE

In its pure form, synthetic psilocybin is a white crystalline material which may be encountered in the form of capsules, tablets, or solution. Crude mushroom preparations containing psilocybin are sometimes distributed either as intact dried brown mushrooms (which remain potent for years) or as powdered material in capsules.

DOSAGE

Medical

Not applicable.

Nonmedical

Dose range is between 1 and 20 mg; however, typical doses are between 4 and 10 mg. To produce psychoactive effects similar to those produced by LSD, approximately 150–200 times the amount (by weight) of psilocybin is needed.

ROUTES OF ADMINISTRATION

Synthetic psilocybin can be taken orally in tablets, capsules, or solution. Psilocybin powder mixed with fruit juice, "fungus delight," is a common form of preparation for oral ingestion. The mushroom itself may be eaten either fresh or dried. Psilocybin may also be sniffed, smoked, or injected. However, injection of crude preparations can involve risk of medical complications resulting from the nondrug materials present.

EFFECTS OF SHORT-TERM USE[1]

CNS, behavioral, subjective: There is fairly wide variation among users in possible perceptual, cognitive, and emotional experiences produced by psilocybin. In addition to the size of the dose, drug effects are also influenced by the setting, the user's expectations, past drug experiences, and personality.

Early effects[2] (which generally occur) include facial numbness, tension and anxiety, rapid reflexes, muscle twitches and muscle weakness, pupillary dilation, and lightheadedness. Later effects can include the following:

1. There may be vivid perceptual distortions, usually visual, such as "pseudohallucinations" and "pseudoillusions."
2. Time may be distorted (minutes may seem to pass as slowly as hours).
3. Space may be distorted.
4. There may be distortions of body image. There may be sensations of heaviness or of weightlessness, the latter resulting in the feeling of floating.
5. Synesthesias frequently occur.
6. There may be a partial or complete loss of recognized boundaries between self and the environment, reactions to which may range from intense pleasure to terror.
7. All sensory experiences tend to be heightened. The user

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[1] 4–10 mg taken orally by nontolerant users. As with LSD, higher doses generally tend to produce quantitative (i.e., more intense) rather than qualitative changes in effects.

[2] Occurring within 15–45 minutes after administration.

perceives brighter colors, sharper definition of objects, increased hearing acuity, more sharply distinguished taste, etc. These heightened sensations may alternate with sensory impairment.

8. Difficulties in concentrating, thinking, and maintaining attention are often experienced.
9. While memory may also be impaired, it is not unusual for past and possibly repressed experiences to be vividly recalled; these may meld with current experiences; a sense of the present reality (the "here and now") may be temporarily lost.
10. There may be intense preoccupation with otherwise trivial thoughts, experiences, or objects.
11. Users may feel that they are undergoing a profound mystical, religious, or "cosmic" experience—for many users perhaps the most desired effect.

A highly adverse reaction to the above ("bad trip") can occur in some users, and may be characterized by the following symptoms: confusion, disorientation, fearfulness of nonexistence or of disintegration of self, inability to distinguish between reality and unreality, paranoid thinking, true hallucinations, possibly severe agitation and/or depression, and panic or even terror.

Cardiovascular (all are early effects): increased blood pressure and heart rate; elevated body temperature and sweating, which may be followed by chills and shivering.

Gastrointestinal: nausea and vomiting (very common); abdominal cramps (all are early effects).

The effects of psilocybin tend to wear off more rapidly than those of LSD, usually within three to six hours after administration.

EFFECTS OF LONG-TERM USE

Because of the rapid development of tolerance to the effects of psilocybin, chronic daily use is unlikely to occur (see Tolerance and Dependence below).

Even one episode with psilocybin has occasionally been known to precipitate a protracted psychotic state similar to paranoid schizophrenia. Some observers have suggested that psychosis is likely only in those users who were latent psychotics prior to the psychosis-inducing event.

Adverse effects directly attributable to chronic use of psilocybin have not been adequately researched.

LETHALITY

There have been no reported deaths known to have resulted from psilocybin overdose. However, severely adverse psychic effects of the drug on some individuals have been known to prompt hazardous or even life-threatening behavior.

TOLERANCE AND DEPENDENCE

Complete tolerance to the psychic effects of psilocybin occurs after the drug has been taken for several consecutive days.[2] After tolerance has developed, no amount of this drug can then produce the desired psychic effects, and the user is compelled to abstain for several consecutive days in order to regain original sensitivity. Nor is it of any use to take such other hallucinogens as LSD or mescaline during the period of abstinence. Each of these drugs produces cross-tolerance to the effects of the other; that is, none can produce the desired effects until after the several-day period of complete abstinence. LSD produces tolerance to its effects even more rapidly than psilocybin.

Neither physical nor psychological dependence has been reported.

PATTERNS OF USE

Mushrooms containing psilocybin and a closely related hallucinogen, psilocin, come chiefly from Mexico, Central America, and some areas of the southern United States.[3] Recently psilocybin and psilocin

[2] See Tolerance—Tachyphylaxis under Drug Tolerance: The Body's Adaptation to Drugs in section 1.

[3] Their use among Indian tribes in Mexico on religious and other ceremonial occasions was common for centuries prior to the invasion of the Spanish conquistadors; they continue to be used to this day by Indians in some remote areas of southern Mexico.

have also been found in some related species of mushrooms indigenous to Australia, Great Britain, Europe, the northwestern United States, British Columbia, and some other areas of Latin America.

Psilocybin is very rarely encountered on the street drug market in most areas of North America. Most street samples presented for laboratory analysis that are alleged to be psilocybin have in fact turned out to be low-dosage preparations of LSD added to ordinary mushrooms or other vegetable matter.

ABUSE POTENTIAL

Because psilocybin is both rarely available in most areas of our society and not known to produce dependence, its abuse potential is extremely low.

REFERENCE

Lewis, W.H., and Elvin-Lewis, M.P.F., *Medical Botany: Plants Affecting Man's Health*, John Wiley and Sons, New York, 1979.

Tricyclic Antidepressants

DRUG CLASS: MOOD MODIFIERS;
ANTIDEPRESSANTS

SYNOPSIS

The tricyclic antidepressants are the most widely used drugs for treating endogenous depression—that is, those forms of depression originating from within rather than arising as a reaction to specific external events. It is thought that there are insufficient amounts of certain chemicals (e.g., norepinephrine and serotonin) in the brains of endogenously depressed patients. The tricyclic antidepressants have been shown to increase the availability of these chemicals to nerve cells in the brain; it is believed that by this action the relative deficiency of the chemicals in endogenously depressed persons is corrected, with resultant mood elevation.

Mood improvement occurs gradually with everyday use of the antidepressants and may not be noticeable until the second or third week of therapy. The physician should inform the patient that improvement does not immediately occur and that the medication must be continued as prescribed for the desired effect to be achieved.

Tolerance to the antidepressant effects of these drugs does not appear to develop (although tolerance does develop to some of the side effects), and physical and psychological dependence reportedly occur only infrequently. Moreover, the tricyclic antidepressants are generally acknowledged to have a very low abuse potential.

DRUG SOURCE

Tricyclic antidepressants are produced through chemical synthesis by the pharmaceutical industry.

TRADE NAMES

Some of the more commonly used tricyclic antidepressants include amitriptyline (e.g., Elavil, Novotriptyn), imipramine (e.g., Novopramine, Tofranil), and doxepin (e.g., Sinequan).

STREET NAMES

None.

COMBINATION PRODUCT

Elavil Plus (amitriptyline and perphenazine[1]).

MEDICAL USES

For the treatment of moderate to severe endogenous depression including that accompanied by anxiety.

PHYSICAL APPEARANCE

Tricyclic antidepressants occur as white crystalline powders soluble in water and in alcohol.

DOSAGE

Medical

For depression, initial daily amounts of 50–100 mg of any of the above are taken in divided doses; the typical outpatient maintenance dose is 100–150 mg per day in divided doses, and the daily dose range is between 75 and 300 mg.

Nonmedical

Some methadone maintenance patients have been known to abuse amitriptyline at daily doses higher than the maximum recommended level; they claim that the combination of this drug and methadone produces tranquility and sometimes a "sedative high."

ROUTES OF ADMINISTRATION

These drugs are usually taken orally by tablet or capsule or in syrup. Intramuscular injection is occasionally used in hospital settings.

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[1] Perphenazine is a phenothiazine (major) tranquillizer.

EFFECTS OF SHORT-TERM USE: LOW DOSES[2]

The desired psychotherapeutic effects of tricyclic antidepressants do not occur after a single drug administration, and usually are not noticeable until the second or third week after commencement of daily antidepressant therapy. Nonetheless, a number of side effects, usually mild, may occur after the initial dose is administered:[3]

CNS, behavioral, subjective: Drowsiness is one of the most common effects and may be desirable for those patients suffering from insomnia. Other effects include dizziness, motor incoordination, concentration difficulties, sedation, fine tremor, blurred vision, ringing in the ears, sometimes confusion and disorientation, and (rarely) seizures.

Cardiovascular: mildly irregular heartbeat; slight increase in heart rate; slight drop in blood pressure particularly when attempting to rise to a standing position; palpitation; headache; sweating.

Gastrointestinal: dryness of the mouth; constipation; nausea and vomiting; stomach discomfort.

Other: allergic reactions; urinary retention; impotence.

EFFECTS OF SHORT-TERM USE: HIGHER DOSES[4]

At higher doses any of the above symptoms may be intensified, and increasingly high doses are accompanied by greater respiratory depression; however, the most important adverse effects are exerted on the brain and the cardiovascular system.

Normal persons, given single doses of 200 mg of imipramine, experience several of the low-dose effects and also feel anxious, clumsy, and unhappy. Furthermore, their performance on a variety of tests is impaired.

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[2] Single dose of 50 mg or less taken orally by nontolerant users.

[3] Because these drugs can lower the seizure threshold and can impair cardiovascular function, caution must be exercised in prescribing them for those patients with a history of epilepsy or cardiovascular disease.

[4] Single doses in excess of the therapeutic range taken orally by nontolerant users, or lower doses in particularly sensitive individuals.

Very high doses (i.e., overdose) can cause a brief period of agitation and excitement, often accompanied by hyperactive reflexes, muscle rigidity, confusion, abnormal sensitivity to light, blurred vision and sometimes hallucinations, muscle twitching, and grand mal seizures. This phase is typically and rapidly followed by stupor or coma and the following: heavy sweating, very rapid heart rate and other cardiovascular abnormalities, high fever (with imipramine overdose) or low body temperature (with amitriptyline and doxepin overdose), depressed reflexes, pupillary dilation, and respiratory depression. Coma may last for a few days and, if the patient survives, is typically followed by a period of excitement and delirium.

At any time throughout the entire drug overdose episode, including the period of excitement and delirium, death may be caused by heart failure arising from severe cardiac arrhythmia.

EFFECTS OF LONG-TERM USE

Tricyclic antidepressants can produce significant mood elevation in those patients suffering from endogenous depression by the second or third week after the onset of therapy. It is essential that the treating physician inform the patient that the desired effects will not be fully experienced before that time; if this information is not imparted, the patient, feeling that the drug is providing little or no benefit, may decide to discontinue taking it before the full therapeutic effects begin. Furthermore, the patient may actually feel worse since the expectation of prompt relief has been disappointed.

Many of the above-noted short-term unwanted effects may persist in patients for extended periods. Those symptoms which most commonly continue to affect the patient include dry mouth, constipation, blurred vision, urinary retention, rapid heart rate, and palpitations. However, with regular daily use of tricyclic antidepressants, the patient usually acquires tolerance to most of the undesired effects.

Daily therapeutic treatment at high doses can cause continuing confusion and disturbed concentration in some patients; transient visual hallucinations may also occur, although rarely. Other symptoms which can be manifested as a result of chronic high-dose therapy include insomnia, restlessness, jitteriness, nightmares, fatigue, tremors, and occasionally disorientation and delusions. Generally, such symptoms disappear or are sharply reduced in intensity if the patient's daily dose is reduced. However, the presence of these symptoms may represent the unmasking of latent schizophrenia, a severe psychotic disorder. In these cases, a combination product such as Elavil Plus, which contains antipsychotic medication, may be effective in managing schizophrenic symptoms without interfering with the desired antidepressant effects.

Weight gain is a common side effect in patients undergoing antidepressant therapy. It is not related to the pharmacological actions of tricyclic antidepressants. Rather, it is typically due to improved appetite which develops as mood generally improves.

LETHALITY

The margin of safety between daily therapeutic doses of tricyclic antidepressants and a single overdose sufficient to produce death can be relatively small. The lowest reported lethal dose is 500 mg, less than twice the maximum therapeutic dose. However, users have been known to survive overdoses of almost 4 grams (4,000 mg).[5] It is generally agreed that patients taking antidepressants are a high-risk suicide group; therefore, when prescribing these drugs only moderate amounts (e.g., a week's supply) should be provided at any given time. Nonetheless, even with cautious prescribing, patients have been known to hoard their drugs and then make serious suicide attempts.

As noted earlier, these drugs have important effects on the heart which may cause patients to experience changes in the heart's rhythm and a fainting feeling associated with decreased blood pressure when rising to a standing position. Moreover, cases have been reported in which heart attacks have occurred or other heart disease has developed during therapy with these drugs. Because of such effects, patients should be carefully screened for a history of heart disorders before tricyclic antidepressants are prescribed.

TOLERANCE AND DEPENDENCE

Tolerance to the antidepressant effect of tricyclic antidepressants

[5] Usually the lethal dose of tricyclic antidepressants is approximately 1,000–2,000 mg.

does not appear to develop even with extended use. There have been occasional reports of physical dependence. The mild withdrawal syndrome after abrupt abstinence involves nausea, headache, muscle aches, runny nose, and a general feeling of physical discomfort. Psychological dependence sometimes develops.

PATTERNS OF USE

The tricyclic antidepressants are very widely prescribed. For example, in the United States, the number of prescriptions written for them either alone or in combination products is almost 25 million per year; the most popular antidepressant is amitriptyline. The principal consumers are women and the elderly.

Patients with a history of drug abuse have been known to increase their daily dose of these drugs excessively. There is also evidence that some methadone maintenance patients abuse them. These patients allege that when taken in combination with methadone, antidepressants can produce tranquility or a pleasant "high." Generally, however, antidepressants are rarely encountered on the street drug market.

ABUSE POTENTIAL

The dependence liability of the tricyclic antidepressants is insignificant, for they do not produce the euphoria apparently necessary to create dependence. It would appear that their abuse potential is very low considering the millions of patients who regularly take them as prescribed in contrast to the few who abuse them.

Section 4

Other Drugs of Interest

Amanita Muscaria

DRUG CLASS: HALLUCINOGEN

Amanita muscaria (fly agaric) is a mushroom which is widespread in the temperate parts of Europe, Asia, and North America. It is also known by the names fly agaric and fly amanita because of the presence of an insecticidal constituent which kills flies exposed to it.

In Europe and parts of Asia, the mushroom has a bright red cap and is mottled with white warts. The North American variety has a yellow, orange-red, or white cap and is mottled with white, red, or yellow warts.

The amanitas are well known for two aspects of their pharmacological activity. Many of them, including *Amanita phalloides* (also known as "deadly amanita," "destroying angel," and "avenging angel") and *Amanita verna*, are highly lethal, apparently because of the presence of certain potent toxins such as phalloin and amanitins. Amanita poisoning is characterized by a long delay (10 hours or longer) between ingestion of the mushrooms and the onset of symptoms. The large majority of mushroom poisonings in North America are due to the amanitas.

Amanita muscaria has markedly lower toxicity than other members of this family and is most commonly associated with hallucinogenic experiences. Indeed, it has been suggested that this mushroom may be the fabled "soma" mentioned in the ancient Vedic writings of India; soma was regarded as a divine intoxicant by the priests, who valued its hallucinogenic properties as a vital part of their religious rituals. It has also been used in Siberia as an inebriant.

Amanita muscaria contains the alkaloid muscarine as a relatively minor component, together with the active principles, ibotenic acid and its more active degradation product, muscimol. The active compound muscarazone has also been found in some specimens. These components are thought to be responsible for the altered state of consciousness which usually begins within a half-hour of ingestion of the mushroom.[1]

Early pharmacological effects include dizziness, nervousness, dry mouth, rapid and deep respiration, diarrhea, nausea and vomiting, muscle twitches, and numbness in the limbs. These are followed by a light and peaceful sleep accompanied by vividly colored imagery. Upon awakening, the user usually experiences a state of mescaline- or psilocybin-like altered perceptions, euphoria, exhilaration, and intense involvement with self as well as an increased ability to perform unusually demanding physical tasks. This period may last for three to four hours. Subsequently, muscle twitching may be noticeable, and CNS-depressant effects gradually develop to the point of ultimate loss of consciousness in the form of deep sleep.

Severe psychological consequences can occur for some users of *Amanita muscaria*, and may include paranoid thinking, outwardly directed violent behavior, bizarre behavior, and self-mutilation.

Deaths occasionally result from ingestion of *Amanita muscaria*, although much less frequently than with other amanitas possibly because much of the mushroom is removed from the body through vomiting and diarrhea. A lethal overdose causes delirium, convulsions, deep coma, and death from cardiac arrest.

It is important to note that amanita mushrooms vary greatly in appearance, and persons who actively seek out *Amanita muscaria* for its mind-altering properties, or who come upon amanitas in their search for *Psilocybe* mushrooms, may inadvertently collect the more toxic amanitas.

[1] The hallucinogenic components of this mushroom are eliminated in the urine without significant loss in potency. For this reason, users in some areas of Siberia have been known to recycle the active constituents several times through repeated consumption of their own urine.

Amyl Nitrite

DRUG CLASS: VASODILATOR

Amyl nitrite ("poppers") occurs as as a clear, yellow, highly volatile and inflammable liquid with a fragrant odor and pungent aromatic taste. It is produced through chemical synthesis.[1]

Amyl nitrite causes relaxation of almost all smooth (involuntary) muscles, including the muscles of all blood vessels. However, it is best known for producing dilation of the blood vessels of the heart, particularly the larger vessels and the collateral vessels; the latter serve as major alternate pathways of essential blood flow when other vessels have become occluded. Because of its action of facilitating blood flow to the heart,[2] amyl nitrite is used therapeutically primarily for relief of severe constricting pain in the chest (angina pectoris) which appears to result from inadequate provision of oxygen to some areas of heart muscle.

Amyl nitrite is prepared in glass-enclosed ampoules. The medical user, at the first indication of an attack, normally crushes the ampoule in the hand, which is protected by a piece of cloth, and immediately inhales the vapors.[3] The effects are felt within 30 seconds and last for no more than two or three minutes. A typical therapeutic dose is approximately 0.2 ml. The principal side effects are transient headache, dizziness, and flushing of the face. Large doses can cause nausea and vomiting, restlessness, abnormally low blood pressure, fainting, coldness of the skin, slowed heart rate, and impaired respiration. A principal hazard of overdose is circulatory collapse.

Amyl nitrite has been subject to abuse by some teenagers because it can cause a quick (although brief) "high" and also because, compared to other drugs of abuse, it is relatively easy to obtain. (The method of administration is the same as for the medical user.) It reportedly produces pleasant perceptual distortions. However, its principal appeal to

[1] It is also used as an industrial solvent. See Inhalants article in section 3.

[2] As well as reducing both peripheral blood flow resistance and the work of the heart.

[3] Hence its street name, "poppers."

nonmedical users lies in its reputation for enhancing sexual performance and orgasm, an effect thought to be caused by its vasodilator properties; nonetheless, its unpredictable effects on the genitourinary tract muscles and other side effects such as headache make its use unattractive to many. It is also potentially hazardous to those with low blood pressure.

Tolerance develops to the vasodilator effects with regular use; however, this drug's capacity for producing dependence is not known.

Amyl nitrite is controlled under the Health Disciplines Act in Ontario. No prescription is required, but it can be sold only by a licensed pharmacist. The buyer must state the purpose for which it is intended and also sign the Poison Register.

Anileridine

DRUG CLASS: NARCOTIC ANALGESIC;
OPIOID

Anileridine (Leritine) is a synthetic narcotic analgesic which occurs as a white crystalline powder freely soluble in water and very soluble in alcohol. This drug is chemically similar to meperidine (e.g., Demerol), although its analgesic potency is substantially greater—approximately three times greater when administered in molecularly equivalent doses. Anileridine is used exclusively for relief of moderate to severe pain; the single therapeutic dose range is 25–50 mg, and it can be taken orally by tablet or given by intramuscular or subcutaneous injection. When these routes of administration are employed, its side effects are generally fewer and milder than those of other potent narcotic analgesics. However, if administered by sudden rather than gradual intravenous injection, even small doses of anileridine (e.g., 10 mg or more) can produce extremely dangerous effects including severe respiratory depression, rapid drop in blood pressure, and cardiac arrest.[1] Such life-threatending consequences rarely occur with small doses of other commonly used narcotic analgesics given by rapid intravenous injection.

The dependence liability of anileridine is similar to that of morphine; however, anileridine is mainly used in hospital settings and is rarely encountered on the street drug market.

[1] Fortunately, these effects can be rapidly reversed by administration of narcotic antagonist drugs such as naloxone.

Atropine, Scopolamine, and Related Alkaloids

DRUG CLASS: ANTICHOLINERGIC AGENTS; HALLUCINOGENS

A number of plants containing the naturally occurring alkaloids atropine, scopolamine, and hyoscyamine are found in many areas throughout the world. Such plants belong to the Solanaceae (potato) family and include *Atropa belladonna* ("beautiful lady"), also known as deadly nightshade, and *Datura stramonium* ("devil's weed," "locoweed"), also known as jimsonweed.

These drugs initially stimulate and then depress both lower and higher brain centres. The atropinic alkaloids have long been used in medicine because they produce several useful effects, including depression of gastric motility and gastric secretion; inhibition of glandular secretions of the nose, mouth, and pharynx; pupillary dilation; paralysis of the muscles of accommodation in the eye; relaxation of smooth-muscle spasms; suppression of tremors associated with Parkinson's disease and other neurological disorders; and slowed heart rate (at low doses). These effects generally occur at dose levels of 1 mg or less. With oral administration, however, only scopolamine has psychoactive effects at such dose levels[1]—mild euphoria, sedation, drowsiness, and sometimes hallucinations and amnesia. Scopolamine has been clinically used as a sedative and occasionally abused for its mild low-dose hallucinogenic effects.

At higher doses (e.g., 10 mg or more), all of these agents produce a number of intense central nervous system (CNS) stimulant effects, including hallucinations; disorientation; confusion; memory loss; paranoid thinking; agitation; speech disturbances; impaired motor coordination; maximal dilation of the pupils; and sometimes convulsions. These effects are usually accompanied by abnormally rapid and irregular heart rate; abnormally high blood pressure; rapid and weak pulse;

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[1] Recently scopolamine has become available in over-the-counter products to combat motion sickness, prepared for transdermal application (i.e., absorbed slowly into the body through the skin). Because of the small amounts of scopolamine and the slow absorption, psychoactive effects are unlikely.

headache; high fever; dry and burning sensations in the mouth; and nausea and vomiting. Flushing of the skin commonly occurs and mimics scarlet fever. The stimulant phase may last for as long as two days, sometimes longer, and is typically followed by a phase of deep sleep or in some cases coma.

Children are particularly sensitive to the effects of these drugs, and doses as small as 10 mg are sometimes fatal to them. Nowadays, however, fatalities among adults are rare and usually result from severe overdose. Lethal overdose is characterized by coma, very high fever, paralysis, cardiovascular collapse, and death from respiratory arrest.

Chloral Hydrate

DRUG CLASS: SEDATIVE/HYPNOTIC

Chloral hydrate (e.g., Chloralex) is a synthetic sedative/hypnotic which occurs as colorless crystals with a pungent odor and a very bitter taste; it is very soluble in both water and alcohol. Chloral hydrate is employed both for sedation and for induction of sleep; the typical sedative dose is 250 mg, usually taken three times per day, and the typical sleep-inducing dose range is between 0.5 and 1.5 grams (500–1,500 mg) before bedtime. Doses in excess of the therapeutic range can produce a state of pleasurable intoxication similar to that produced by alcohol or barbiturates. Some highly tolerant abusers reportedly take as much as 10–12 grams per day. The main dangerous effect of very high doses (overdose) of this drug is respiratory depression.

When taken in therapeutic doses, chloral hydrate possesses several advantages over barbiturates and most other clinically used sedative/hypnotic drugs:

1. Chloral hydrate produces fewer and milder residual effects (persistence of intoxication or sedation), since it and its major psychoactive metabolite are more rapidly eliminated from the body than most drugs in this class.
2. REM sleep is minimally affected by sleep-inducing doses.[1]
3. Therapeutic doses have a negligible effect on respiration.
4. Its dependence liability is not as great as that of most other drugs used for essentially the same purposes, for the pleasurable intoxication it produces is generally less intense.

The principal drawbacks of this agent are its propensity for causing gastric distress (resulting in nausea and vomiting) and its disagreeable taste; the noxious effects, however, are usually insignificant when chloral hydrate is taken in capsules along with sufficient quantities of milk or water. Nonetheless, taking high doses on a regular basis can cause such serious consequences as gastric hemorrhage.

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[1] See Central Nervous System Depressants chapter (section 2) for discussion of the significance of REM sleep.

Chronic use/abuse of chloral hydrate results in the acquisition of tolerance to the effects desired, and thus the user may resort to ever higher daily doses in order to maintain the original intensity of effects. However, appreciable tolerance to the respiratory-depressant effects produced by higher doses does not develop. Therefore, with progressively higher daily doses the margin of safety is reduced, and death can ultimately result from respiratory arrest. The margin of safety can also be significantly reduced if high doses of chloral hydrate are taken in combination with such other CNS depressants as alcohol or barbiturates.

Physical dependence on chloral hydrate can develop when abusive daily doses are taken for protracted periods of time. Abrupt discontinuation of use may then cause a severe withdrawal reaction resembling alcoholic withdrawal, with symptoms including delirium tremens and sometimes convulsions.

Diphenoxylate

DRUG CLASS: NARCOTIC ANALGESIC; OPIOID

Diphenoxylate (Lomotil) is a weak synthetic narcotic analgesic which occurs as a white crystalline powder almost insoluble in water and slightly soluble in alcohol. The only medical use for diphenoxylate is for symptomatic relief of diarrhea; the single therapeutic dose is 5 mg taken orally, usually three to four times per day. At such a dose level, diphenoxylate exerts little or no euphoric or analgesic effects. The most common side effects of a therapeutic dose include mild nausea, vomiting, drowsiness, lethargy, sedation, and dizziness. However, at higher dose levels (e.g., 40–60 mg), this drug can produce typical narcotic analgesic effects and can also partially suppress withdrawal symptoms produced by abrupt abstinence from other narcotic analgesics.

Chronic use of diphenoxylate at the typical daily dose level does not appear to produce physical dependence, although regular high-dose abuse can result in the development of a mild form of physical dependence. Nonetheless, diphenoxylate and its salts differ from the commonly abused narcotic analgesics in that the former are almost insoluble in water and therefore cannot be injected. Since diphenoxylate is also relatively less potent than other narcotic analgesics, it is unattractive to narcotic analgesic abusers, who are likely to resort to it only when their preferred drugs are not available.

Severe overdose of diphenoxylate can produce symptoms similar to those resulting from overdose of other narcotic analgesics; these symptoms include coma, severe respiratory depression, and cardiac arrest. Young children may exhibit such symptoms after having consumed doses as small as 30–50 mg.

DMT

(Dimethyltryptamine)

DRUG CLASS: HALLUCINOGEN

DMT is structurally similar to psilocin, a hallucinogenic alkaloid found in the *Psilocybe* and *Conocybe* species of mushroom. As a pure substance, DMT is available as a white crystalline product of laboratory synthesis. However, together with a number of closely related chemicals, it is a naturally occurring component of several plants (e.g., *Piptadina peregrina*) found in the West Indies and South America, and has been used by South American Indians for centuries in the form of snuffs for its hallucinogenic effects. These effects were first noted by Europeans in 1496 during the second voyage of Columbus to the West Indies.

The traditional use of these plant materials in the form of snuffs is particularly interesting, because we know that DMT and closely related chemicals are far more active when inhaled or injected than when taken orally.[1] For this reason, in North America DMT has often been encountered in marijuana preparations, the marijuana having been soaked in a solution of DMT and then dried. Taken alone, doses of approximately 50–60 mg (injected or inhaled) can produce a spectrum of psychological and physical effects similar to those produced by such other hallucinogens as LSD and mescaline. The effects are perceived rapidly, and, unlike with other hallucinogens, the entire hallucinogenic episode is quite brief, lasting for 30–60 minutes (hence its street name "businessman's lunch"). Anxiety and nonpsychotic panic states tend to be induced more frequently by DMT than by most other common hallucinogens. Some investigators have suggested that the anxiety may be due to the very rapid onset of this drug's potent effects; that is, the user does not have sufficient time to acclimatize to the dramatic shift in subjective experience.

Physical dependence on DMT does not appear to develop. Whether or not tolerance develops fully to the subjective effects has yet to be demonstrated. In one recent research study, normal subjects, given two daily intramuscular injections of DMT for a period of five days, exhibited only partial tolerance to the subjective effects. Furthermore, recent evidence suggests that DMT does not produce cross-tolerance with LSD (although mescaline and psilocybin do). DMT may therefore have a somewhat different mechanism of action than these other hallucinogens.

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[1] Even large doses of DMT taken orally (e.g., 350 mg) fail to produce any significant effects.

Ephedrine

DRUG CLASS: CNS STIMULANT

Ephedrine is a naturally occurring central nervous system stimulant obtained from the plant *Ephedra equisetina.* It is now also produced by chemical synthesis, the synthetic product being marketed in the form of its sulfate salt, ephedrine sulfate; this salt occurs as a white crystalline powder with a bitter taste, soluble in water and very soluble in alcohol. Ephedrine is closely related in structure to methamphetamine, although its CNS actions are much less potent and also longer-acting than those of the amphetamines. Its peripheral stimulant actions are similar to but less powerful than those of epinephrine (also called adrenaline), a hormone produced in the body by the adrenal glands.

Ephedrine has moderately potent bronchial muscle relaxant properties, and therefore is used for symptomatic relief in milder cases of asthmatic attack; it is also used to reduce the risk of acute attacks in the treatment of chronic asthma. The typical adult dose range is 25–50 mg taken orally, three to four times per day, in the form of tablets. Ephedrine in the form of nose drops is also widely used to relieve nasal congestion associated with upper respiratory tract illnesses. It is also used to treat low blood pressure, because it constricts blood vessels and stimulates certain actions of the heart. Common side effects are qualitatively similar to those produced by amphetamines and are generally milder.[1] Higher doses (overdose) can cause restlessness and anxiety, dizziness, insomnia, tremor, rapid pulse, sweating, respiratory difficulties, confusion, hallucinations, delirium, and (infrequently) convulsions. The elderly are particularly sensitive to overdose, and there have been a few deaths among such patients.

Tolerance develops to the main effects of ephedrine; however, temporary abstinence restores sensitivity.

Because of ephedrine's stimulant properties, it is one of the substances forbidden to athletes in sports events in which the use of most stimulant drugs is prohibited; its presence can be detected in a urine test.

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[1] See Amphetamines article in section 3.

Ephedrine has some abuse potential, although stimulant abusers prefer more powerful drugs when they can obtain them. Recently, ephedrine has been found in a number of street preparations in combination with a similar drug, phenylpropanolamine, and caffeine. Many of the preparations superficially mimic the appearance of legitimate pharmaceutical products, particularly amphetamines. Such samples have turned up in several areas of the United States and in southern Ontario.

Ethchlorvynol

DRUG CLASS: SEDATIVE/HYPNOTIC

Ethchlorvynol (Placidyl) is a rapid-acting synthetic sedative/hypnotic which occurs as a colorless to yellow liquid with a pungent odor and a slightly bitter taste; it is insoluble in water and forms a suspension with alcohol. It is clinically used for sleep induction and, infrequently, for daytime sedation. The typical sedative dose is 200 mg taken three times daily, and the typical sleep-inducing dose ranges between 0.5 and 1.0 grams (500–1,000 mg) before bedtime. Effects may be perceptible within 15–30 minutes after oral administration by capsule. Doses of ethchlorvynol in excess of the therapeutic range can produce a state of pleasurable intoxication similar to that produced by alcohol or barbiturates. Highly tolerant abusers have been known to take daily doses substantially in excess of the therapeutic range. The principal hazardous effects of very high doses (overdose) of ethchlorvynol are respiratory depression and abnormally low blood pressure.

When ethchlorvynol was introduced, it was reported to be an effective and safe alternative to the barbiturates. However, it does not appear to possess any special therapeutic advantages over the barbiturates, and, in fact, presents significant liabilities in its own right. With nightly use, tolerance develops rapidly (within a few weeks) to the sleep-inducing effects. Other effects desired by users/abusers, such as sedation and euphoria, are also subject to the rapid acquisition of tolerance; however, as with the barbiturates, appreciable tolerance does not develop to the respiratory-depressant effects produced by higher doses. Therefore, those who systematically increase the size of their daily dose to compensate for acquired tolerance also unwittingly increase the risk of life-threatening consequences. Death has resulted from an overdose of 7 grams (7,000 mg), although people have survived much greater overdoses. The risk of fatality can be significantly increased if an overdose is accompanied by ingestion of such other CNS depressants as alcohol or barbiturates.

Physical and psychological dependence can result from chronic use of this drug. Withdrawal sickness has occurred after abrupt termination of use even when the daily dose has been as small as 1 gram (1,000 mg). Withdrawal symptoms may include agitation; nausea and vomiting; insomnia and other sleeping difficulties; slurred speech; tremor; motor incoordination; and loss of appetite. Toxic psychosis similar to acute schizophrenia, delirium, and convulsions sometimes occur.

The dependence liability of ethchlorvynol is similar to that of the short- or intermediate-acting barbiturates; however, its potential for abuse is lower because it is much less widely prescribed. It is infrequently encountered on the street drug market.

Fenfluramine

DRUG CLASS: ANOREXIANT

Fenfluramine (e.g., Ponderal) is a pharmaceutically manufactured synthetic anorexiant (appetite suppressant) which occurs as a white odorless crystalline powder with a slightly bitter taste; it is soluble in water and in alcohol. It is used clinically as a diet pill for the short-term management of obesity arising from poor dietary habits. The typical therapeutic dose is 20–40 mg, which is taken orally by tablet three times per day. Certain common side effects of therapeutic doses of fenfluramine differ from those of amphetamine and other appetite suppressants. At such dose levels fenfluramine generally does not produce significant psychomotor stimulant actions, and indeed often produces drowsiness, sedation, lethargy, and fatigue (although the more typical stimulant effects—anxiety and insomnia—sometimes occur). Other common side effects include dizziness, slight drop in blood pressure, dry mouth, nausea and vomiting, diarrhea, and increased urinary output.

Because high doses of fenfluramine can produce euphoria, hallucinogen-like perceptual changes, and feelings of unreality, fenfluramine has often been abused. However, most abusers claim that its euphoric effects are not powerful; therefore, it is rarely their first choice of drug. The principal hazards of very high doses (i.e., overdose) include very high fever, convulsions, and severe cardiovascular dysfunction. Fenfluramine overdose has caused a number of deaths, usually from heart failure.

In most cases, tolerance rapidly develops to the undesired side effects produced by therapeutic doses; tolerance to the appetite-suppressant effect usually develops within 8–12 weeks. If users wish to maintain the desired intensity of the latter effect, higher daily doses then become necessary. Because both tolerance and psychological dependence can result from chronic use, protracted and regular administration is medically ill-advised. Physical dependence on fenfluramine seems to occur in some users; when withdrawal does occur after abrupt abstinence, it is manifested mainly as psychic depression.

The dependence liability of fenfluramine appears to be much lower than that of amphetamine and such other diet pills as diethylpropion (e.g., Tenuate), and its abuse potential also appears to be somewhat lower.

Haloperidol

DRUG CLASS: MAJOR TRANQUILLIZER;
ANTIPSYCHOTIC;
ANTIEMETIC

Haloperidol (Haldol) is a powerful antipsychotic drug which is produced by chemical synthesis. It occurs as a white to faintly yellow microcrystalline powder, which is odorless and tasteless and moderately soluble in water and alcohol. Haloperidol can be used for essentially the same purposes as the phenothiazines[1] (although it is structurally dissimilar to them). These purposes include the management of the acute and chronic symptoms associated with schizophrenia (e.g., for controlling delusions, hallucinations, and agitation) and for calming mania associated with manic-depressive psychosis, as well as for controlling aggressiveness and agitation in organically brain-impaired and mentally retarded patients. As an antiemetic (nausea suppressant) haloperidol is used principally in obstetrics during labor.

Haloperidol is more potent than most of the phenothiazines. However, although smaller doses of this drug can produce most of the same desired effects, it lacks the sedative action of many of the phenothiazines. The typical oral dose range is between 1 and 6 mg three times daily, and the typical dose range for intramuscular injection is between 2.5 and 5.0 mg three times daily. Higher doses are used in severe cases. The most common side effects are neurological and include motor restlessness (i.e., a compelling need to constantly move about that is not due to psychic agitation), uncontrollable facial grimacing, stiff neck, speech difficulties, and parkinsonism-like symptoms such as tremors and muscle rigidity. These effects can be partially, or even fully, controlled in many cases by reducing the patient's daily dose of haloperidol or by the introduction of other medications.[2]

The incidence of cardiovascular irregularities, blood disorders (e.g., jaundice), and adverse skin reactions seems to be lower with haloperidol than with the phenothiazines. Furthermore, a neurological

[1] E.g., chlorpromazine. Haloperidol can be substituted for phenothiazines when the latter produce hypersensitivity reactions.

[2] E.g., antiparkinsonism agents.

disorder called tardive dyskinesia (which is sometimes irreversible) occurs less frequently in patients maintained on high doses of this drug than in patients taking high doses of phenothiazines. The condition is characterized by rhythmic involuntary movements of the jaw, face, tongue, and/or mouth, sometimes accompanied by involuntary movements of the limbs.

Tolerance does not appear to develop to the antipsychotic effects of haloperidol, and, as with the phenothiazines, the incidence of physical dependence is very low.

Deaths exclusively due to haloperidol overdose are uncommon; however, when an overdose is taken in combination with other drugs which produce central nervous system depression (e.g., alcohol, barbiturates), the probability of serious consequences is greatly enhanced.

Harmaline and Harmine

DRUG CLASS: HALLUCINOGENS

Harmaline and a closely related alkaloid, harmine, are naturally occurring hallucinogens found in the bark of the South American vine *Banisteriopsis caapi* and other members of the *Banisteriopsis* genus. They can also be obtained from the seeds of the Middle Eastern shrub *Peganum harmala* (also known as Syrian rue). Both have central nervous system (CNS) stimulant properties and are monoamine oxidase inhibitors.[1] The hallucinogenic dose range for experienced users of harmaline is estimated to be approximately 300–400 mg when taken orally and 70–100 mg when injected intravenously; for harmine, the estimated dose ranges are twice as great.[2]

Early effects produced by these drugs include nausea and vomiting, sweating, weakness, dizziness, tremors, and numbness in the limbs. Users then become physically relaxed and tend to lose interest completely in their surroundings. Eyes are usually kept closed, and users experience long dreamlike sequences of vivid images and fantasies, dominated by specific intense colors (usually blues, greens, and purples). Perceptions of the external environment are usually not as greatly affected as with other hallucinogens, and delusions and feelings of unreality generally do not occur. Furthermore, unlike most other hallucinogens, harmaline and harmine do not appear to exert significant effects on thought processes. The experience tends to be highly individualized and usually involves little social interaction. The duration of hallucinogenic activity is approximately six hours.

Preliminary psychiatric research on the content of the visual imagery induced by harmaline suggests that, irrespective of the highly "personal" nature of the hallucinogenic episode, certain archetypal and mythical images connoting aggression and sexuality seem to appear recurrently. These intense images are experienced by such divergent groups as primitive South American Indians and some middle-class South Americans.[3]

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[1] See Monoamine Oxidase (MAO) Inhibitors article below.

[2] Higher doses can result in very distressing hallucinations and delirium.

Because harmaline and harmine are monoamine oxidase inhibitors, they can produce severe and potentially lethal effects on the heart and blood pressure when taken concurrently with any of a wide range of common foods containing tyramine (e.g., aged cheeses, chocolate, red wine) or with CNS-depressant drugs.

Their ability to produce tolerance and dependence with regular use is not known. They have rarely been used in North America, although harmaline was experimentally employed for a short period as an adjunct to psychotherapy.

[3] Many South American Indian tribes in the Amazon Basin have ceremonially used these drugs for centuries, consuming them in beverages.

Hydrocodone

DRUG CLASS: NARCOTIC ANALGESIC; OPIOID

Hydrocodone (e.g., Hycodan) or dihydrocodeinone is a synthetic narcotic analgesic which occurs as a fine white crystalline powder soluble in water and slightly soluble in alcohol. It is structurally similar to codeine, although it is much more potent. Traditionally, hydrocodone has been employed in clinical medicine only as a cough suppressant (antitussive) even though it has powerful analgesic properties. Most hydrocodone preparations are marketed in combination with antihistamines (e.g., Novohistex DH; Congestex DC) in order to combat the congestion accompanying moderately severe to severe cough. A typical therapeutic dose is 5 mg of hydrocodone,[1] administered orally once every four hours. However, some highly tolerant abusers claim to take as much as 250–300 mg of hydrocodone per day.

When taken orally in doses well in excess of the therapeutic level, hydrocodone produces relatively powerful euphoric and sedative effects, although these effects are not as great as those produced by other narcotic analgesics of abuse administered by injection (e.g., heroin, morphine). Nonetheless, hydrocodone appears to be gaining popularity among street drug abusers because it possesses several advantages over the illicit needle drugs:

1. Hydrocodone is more easily obtained, either by forged or legitimate prescription or by pharmacy theft.
2. It is more consistently available, although almost always illegally.[2]
3. The quality (purity) of hydrocodone products prepared by the legitimate pharmaceutical industry is highly consistent.

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[1] And of hydrocodone in combination products.

[2] In Canada, it is a criminal offence for a patient to willfully omit reporting to a prescribing physician any other prescriptions obtained for a narcotic analgesic during the past 30 days.

The above advantages are particularly important to the physically dependent hydrocodone abuser who is constantly seeking to avoid withdrawal sickness. Greater access to hydrocodone contrasts with the difficulties encountered by physically dependent heroin abusers, who must rely on street purchases. Street heroin addicts continuously risk being "burned" (cheated) or having their illicit sources completely dry up; therefore, unlike the hydrocodone abuser, the heroin abuser cannot avoid periodic withdrawal sickness.

4. Hydrocodone abusers reduce the risk of detection by legal authorities, doctors, and others because they do not have "trackmarks" and other evidence of superficial tissue damage associated with chronic needle administration.
5. Hydrocodone abusers do not suffer the severe social stigma which invariably attaches to heroin abusers.

It is therefore not surprising that preliminary evidence indicates a recent trend toward increasing abuse of hydrocodone and those other potent narcotic analgesics which retain much of their efficacy when taken orally, such as oxycodone (e.g., Percodan) and hydromorphone (Dilaudid).

Tolerance can rapidly develop to the desired effects of hydrocodone and other orally administered narcotic analgesics when they are regularly abused; thus, ever higher daily doses become necessary in order to maintain the original intensity of these effects. Powerful dependence can arise from long-term abuse, and abrupt abstinence can cause a morphine-like withdrawal sickness, although it is less severe than that produced by abrupt abstinence from morphine.

A life-threatening overdose of hydrocodone can produce coma, severe respiratory depression, and cardiovascular collapse. The lethal overdose for adults is estimated to be between 0.5 and 1.0 gram (500–1,000 mg).

Ketamine

DRUG CLASS: DISSOCIATIVE ANESTHETIC

Ketamine (Ketalar) is a synthetically manufactured dissociative[1] anesthetic with potent hallucinogenic and analgesic features similar to those produced by phencyclidine (PCP). It occurs as a white crystalline powder, freely soluble in water and soluble in alcohol. When it is injected intravenously over a period of one minute, dissociative feelings are experienced very rapidly and unconsciousness may be achieved almost immediately. The therapeutic intravenous dose range is between 1 and 2 mg per kilogram of body weight (i.e., 70–140 mg for a 150-lb adult); the dose range for intramuscular injection is approximately three times as great. A therapeutic dose causes increased heart rate and elevated blood pressure.

Unconsciousness lasts for only 10–15 minutes;[2] for this reason, ketamine is useful only in short surgical procedures (usually those involving the head and neck where the use of an anesthetic mask is inconvenient) and for induction of anesthesia before switching to another anesthesic. A number of problems associated with its use can further limit its therapeutic value: unsatisfactory muscle relaxation; increased muscle tone; unpredictable and sometimes violent jerking and twitching (which can be precipitated by otherwise relatively innocuous stimuli); vivid and unpleasant dreams during and after surgery; and slow recovery from anesthesia (up to several hours). During the period of recovery, patients may experience headache, nausea and vomiting, hallucinations, feelings of unreality, confusion, and sensations of heaviness or floating. Irrational behavior may also occur. Hyperexcitability (and sometimes convulsions) may be precipitated by even mild stimuli for up to several hours after surgery. These adverse effects are particularly common in patients over the age of 30; nonetheless, some patients find the hallucinogenic effects to be pleasant. The incidence of adverse effects is low among children.

[1] In this context, dissociative means producing feelings in the user of dissociation (or detachment) from the external environment.

[2] Intense analgesia lasts for up to 40 minutes.

Ketamine has been subject to some abuse in both the United States and Canada. Street preparations include powders, capsules, tablets, crystals, and solutions. Nonmedical users inject (estimated) doses of 50 mg or sniff between 60 and 100 mg. At such dose levels, consciousness is usually maintained. The main desired effects are euphoria and "mystical" revelations, as well as hallucinations and pleasant sensations of both floating and stimulation. Users generally experience impairment of cognitive processes, dizziness, motor incoordination, slurred speech, and confusion. Severe adverse episodes ("bad trips") sometimes occur and resemble the toxic psychotic state caused by PCP. The principal hazardous effect of high doses is respiratory depression.

There has been little research on the protracted nonmedical use of ketamine, and it is not known whether tolerance or dependence develops with regular use. However, a number of regular users do experience "flashbacks" (recurrences of psychic events which originally occurred during a ketamine-taking episode). In fact, there are reliable reports of some patients' experiencing recurrent hallucinations after ketamine anesthesia.

Levallorphan

DRUG CLASS: NARCOTIC AGONIST/ANTAGONIST

Levallorphan (Lorfan) is a synthetic narcotic antagonist which also possesses potent narcotic agonist properties.[1] It occurs as a white odorless crystalline powder which is very bitter to the taste and is soluble in water and slightly soluble in alcohol. When narcotic analgesics are not present in the body, a typical therapeutic dose of levallorphan (i.e., 1 mg administered in injection to a nontolerant person) produces an analgesic effect equivalent to approximately 10 mg of morphine; levallorphan is thus a powerful analgesic in its own right. Most people receiving this drug also experience drowsiness and relaxation; however, dysphoric reactions, such as anxiety and fearfulness, occur in many. Others compare the effects of a therapeutic dose to a state of alcohol intoxication and grogginess. Additional common side effects include dizziness, blurred vision, pupillary constriction, mild respiratory depression, nausea, upset stomach, and sweating.

At doses higher than therapeutically indicated, psychotic-like effects may occur; these can include bizarre dreams, feelings of unreality, visual hallucinations, and disorientation.[2] Serious overdose can cause coma, respiratory depression, lowered body temperature, abnormally low blood pressure, and slowed heart rate; toxic psychosis may precede coma.

Levallorphan is principally used medically to counteract (i.e., antagonize) the adverse effects of narcotic analgesics. It can rapidly reverse most narcotic analgesic effects including such hazardous overdose effects as respiratory depression; furthermore, narcotic-analgesic-induced respiratory depression can be reversed or prevented by appropriate doses without significant loss of analgesia.[3] Therefore, it can be particularly useful in pre- and post-operative situations, as well as

[1] The subject of narcotic agonist and antagonist actions is discussed in the Narcotic Analgesics chapter in section 2.

[2] These effects may also occur at therapeutic doses in some particularly sensitive individuals.

[3] Levallorphan can also in some circumstances be used alone for relief of severe pain.

during surgery and labor. However, levallorphan (and other narcotic antagonists, such as naloxone) cannot reverse or prevent respiratory depression caused by overdose of other classes of drugs such as sedative/hypnotics. Caution must be exercised in administering this drug to patients addicted to narcotic analgesics, for it can provoke in them a severe withdrawal reaction.

Tolerance does not appear to develop to the narcotic antagonist effects of this drug when it is chronically taken, although tolerance does develop with regard to the agonistic (e.g., analgesic) effects. Because of the adverse psychological consequences associated with its use at higher doses, levallorphan is rarely abused.

Lithium Carbonate

DRUG CLASS: ANTIMANIC

Lithium carbonate (e.g., Lithane) is a synthetically manufactured drug which occurs as a white odorless crystalline powder with a slightly alkaline taste, slightly soluble in water and insoluble in alcohol. It is used in psychiatry to calm manic episodes in manic-depressive patients. The daily dose range for inpatients is between 1,200 and 2,700 mg in divided doses, and for outpatients 900–1,500 mg in divided doses; it is taken orally in the form of tablets or capsules. Manic episodes are generally characterized by hyperactivity, flights of ideas, extreme and often compulsive talkativeness, highly accelerated rate of speech, excessive elation, and irritability. Lithium carbonate can often reduce such behavior to normal levels within a week or less. Patients may then be chronically maintained on lower doses in order to reduce the probability of recurrent manic episodes.

The most common early side effects include gastrointestinal discomfort, nausea, vertigo, muscle weakness, and a dazed feeling. These effects usually disappear with regular use. More persistent side effects include fine tremor in the hands, as well as fatigue, thirst, and excessive urination.

Lithium carbonate can accumulate in the body with regular use, and higher blood concentrations may produce a serious toxic reaction; early signs of lithium carbonate intoxication include sluggishness, drowsiness, coarse tremors, muscle twitching, loss of appetite, vomiting, and diarrhea. When these effects occur, it is essential to discontinue lithium carbonate therapy immediately, because still higher blood levels can produce life-threatening effects.

Lithium carbonate differs from other drugs used in the management of manic episodes, such as phenothiazines—and, in fact, from all other drugs used in psychiatry—in that in therapeutic doses it produces no discernible psychoactive effects in normal individuals. Another unusual aspect of this drug is its effect on patients after the manic episode subsides; the same high therapeutic doses which were well tolerated during the episode can cause toxic reactions after mania is brought under control. Therefore, patients undergoing lithium carbonate therapy require very careful observation.

Methyprylon

DRUG CLASS: SEDATIVE/HYPNOTIC

Methyprylon (Noludar) is a synthetic sedative/hypnotic which occurs as a white or almost white crystalline powder with a burning taste and a bitter aftertaste; the powder is soluble in water and very soluble in alcohol. The drug is clinically used only for sleep induction, and the typical bedtime dose is 300 mg.[1] It produces fewer and milder side effects than the barbiturates or most other sleep-inducing (hypnotic) drugs. The hypnotic potency of the typical dose is similar to that of 200 mg of secobarbital. The principal adverse side effects of a therapeutic dose are morning hangover and suppression of REM sleep—i.e., those recurring periods of sleep characterized by continuous oscillation of the eyeballs, deep relaxation of the skeletal muscles, and constant dreaming.[2] The main hazardous effects of very high doses (overdose) are abnormally low blood pressure, shock, and excessive secretion of fluids in the lungs (pulmonary edema).

Methyprylon produces less euphoria than the barbiturates and is generally less toxic, although an overdose as small as 6 grams (6,000 mg) has caused death. However, when used nightly, tolerance to its sleep-inducing effects can develop as rapidly as for the barbiturates—that is, within a few weeks. Some users increase the size of their nightly dose in order to maintain the original intensity of the desired effects. There have been recorded cases of highly tolerant abusers taking up to 12 grams (12,000 mg) every 24 hours.

Physical and psychological dependence can result from chronic use of this drug. Withdrawal symptoms after abrupt termination of regular use include insomnia and other sleep-related problems (e.g., REM "rebound"), anxiety, restlessness, and loss of appetite. More severe symptoms have been observed after abrupt discontinuation of chronic high-dose use; these include confusion, hallucinations, and convulsions. At least one fatality has been reported to have occurred during severe withdrawal.

[1] Taken orally by capsule or in liquid suspension.

[2] For further discussion of the significance of REM sleep, see the Central Nervous System Depressants chapter in section 2.

Monoamine Oxidase (MAO) Inhibitors

DRUG CLASS: ANTIDEPRESSANTS;
ANTIHYPERTENSIVES

The group of drugs known as monoamine oxidase (MAO) inhibitors includes a variety of substances which differ in chemical structure. A number of these agents have important antidepressant (mood-elevating) effects and are clinically used for that purpose: isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate).[1] However, significant problems associated with their use limit the scope of their therapeutic application.

MAO inhibitors share the common property of blocking the activity of MAO, a naturally occurring enzyme in the body. This enzyme metabolizes certain other naturally occurring substances in the body (norepinephrine and related compounds) and the monoamines found in a variety of common foods (e.g., aged cheeses, chocolate, red wine, beer, yeast products, citrus fruits). It also metabolizes a number of common drugs, such a sedative/hypnotics, amphetamines, and tricyclic antidepressants. Because MAO inhibitors interfere with the activity of MAO, they indirectly interfere with the metabolism of the aforementioned substances. Serious consequences for the patient can ensue. For example, tyramine is a monoamine found in fermented foods and in particularly large amounts in aged cheese. Sufficient quantities of tyramine, if not adequately metabolized by MAO, can produce severely elevated blood pressure (hypertensive crisis) and other cardiovascular irregularities, effects which can be life-threatening. Furthermore, drugs which are normally metabolized by MAO will, in the absence of MAO, produce more intense, long-lasting, and sometimes dangerous effects. For these reasons, it is essential that patients be fully informed as to which foods and drugs should be avoided or used sparingly while undergoing MAO-inhibitor therapy.

MAO inhibitors can produce disturbing side effects even when patients carefully monitor their food and drug intake. Common side effects include drop in blood pressure when rising to a standing position (causing dizziness and a fainting feeling), abnormally rapid heartbeat, palpitations, dry mouth, upset stomach, constipation, anxiety, and insomnia. Therapeutic doses can produce high blood pressure in some patients even when they avoid inappropriate foods and drugs.

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[1] The typical daily dose range of Parnate is 20–30 mg in divided doses.

Generally, the MAO-inhibitor antidepressants offer no special advantages over the tricyclic antidepressants.[2] In view of the numerous problems associated with their use, they are much less frequently prescribed than the latter group of drugs. The MAO inhibitors are most often used when tricyclic antidepressant therapy and other forms of therapeutic intervention such as electroshock therapy have failed to provide the desired results.

[2] See Tricyclic Antidepressants article in section 3.

Morning Glory Seeds

DRUG CLASS: HALLUCINOGEN

The seeds of members of the Convolvulaceae (morning glory) family—*Rivea corymbosa* and *Ipomoea violacea*—have long been used in the sacred rituals of certain Mexican Indian tribes for their hallucinogenic effects. These seeds contain several forms of lysergic acid amide which are structurally similar to LSD.[1] The principal psychoactive components include d-lysergic acid amide (ergine) and d-isolysergic acid amide (isoergine). These alkaloids are substantially less potent than LSD, ergine being approximately one-tenth as potent in doses of equal weight. However, when taken in sufficient quantities, they produce a range of effects quite similar to those produced by LSD (although nausea, vomiting, and diarrhea are far more common with morning glory seeds). Approximately 100 seeds of, for example, *Rivea corymbosa* contain a hallucinogenic dose of these alkaloids comparable to 100 micrograms of LSD.

The traditional preparation involves pulverizing the seeds and then pouring the resultant powder into cold water. The solution is passed through a filter in order to remove impurities and is then drunk. Grinding the seeds is essential, because the hard impervious coats would otherwise allow the seeds to move unaltered through the gastrointestinal tract.

Morning glory seeds became popular and easily available substitutes for LSD during the 1960s and early 1970s, and nursery growers' exotic trade names—Heavenly Blue, Flying Saucer, Pearly Gates—inadvertently served to enhance their image as hallucinogens. Nowadays most seeds sold for horticultural purposes are coated with insecticides and/or fungicides which are extremely difficult to remove and cause considerable discomfort if ingested (although they are not dangerously toxic to humans). These toxic agents therefore serve as a deterrent against the use of morning glory seeds as a drug.

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[1] Certain other members of the Convolvulaceae family also contain the same alkaloids —e.g., *Argyreia nervosa* (Hawaiian baby woodrose).

Nitrous Oxide

DRUG CLASS: GENERAL ANESTHETIC

Nitrous oxide ("laughing gas," "gas") is a colorless, nonflammable gaseous general anesthetic with a pleasant odor and sweet taste. It has a very rapid onset of action and can relieve pain even at subanesthetic doses. Furthermore, it does not produce the local irritation associated with many other agents which are employed for the same purposes, and it has little or no effect on respiration and cardiovascular functions. However, its usefulness is limited, for the highest concentration of nitrous oxide which can be safely administered without significant risk of hypoxia (oxygen deprivation)[1] is in a ratio of 70% nitrous oxide to 30% oxygen. In this concentration, nitrous oxide is not sufficiently potent in most cases to achieve a satisfactory level of surgical anesthesia. Therefore, it is employed in surgery almost exclusively to supplement other more potent volatile liquid anesthetics, such as halothane, methoxyflurane, enflurane, or ether. It is also widely used in dentistry because it has a high analgesic potency at subanesthetic concentration levels, and because it can produce sedation and relaxation. These last effects are particularly significant, for apprehension is a major component in the overall subjective reaction to painful stimuli.

Nitrous oxide has been abused for more than a century for the pleasurable psychoactive effects it creates. Inhalation can produce euphoria, numbing of the body, giddiness and uncontrolled laughter, sensations of floating, perceptual distortions, and hallucinations. Some users, however, experience anxiety or panic. All of the above effects wear off within a few minutes after discontinuing inhalation. There have been a few reported cases of abuse among medical personnel and several reported deaths among unsophisticated users. Little is known about the effects of long-term use, including tolerance and dependence issues.

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[1] Severe oxygen deprivation (anoxia) can cause irreversible brain damage and death.

Nutmeg

DRUG CLASS: HALLUCINOGEN

Nutmeg, the common household spice, is also a naturally occurring hallucinogen. Nutmeg is the seed of the East Indian tree *Myristica fragrans*, and has been used for its psychoactive and alleged aphrodisiac effects for centuries in some areas of Southern Asia. The psychoactive principle is thought to be myristicin. A hallucinogenic dose ranges between 5 and 10 grams—approximately one teaspoonful, the equivalent of one to two nutmegs. Ground nutmeg, a course brown powder, may be taken alone, in a tea solution, or sniffed. Its psychoactive actions are usually experienced gradually, and two to five hours often pass before the full effects are perceived. Nutmeg intoxication can produce lethargy, marijuana-like euphoria, lightheadedness, uncontrolled giggling and laughter, feelings of detachment from one's surroundings, feelings of unreality, and sensations of either heaviness or floating. Distortions of time and space are frequent manifestations. Other perceptual distortions may also occur, although hallucinations are infrequently experienced at this dose level. Some users claim that nutmeg enhances sexual potency.

Hallucinogenic effects are typically preceded by severe nausea and vomiting, as well as diarrhea and transient headache. Other physiological effects can include increased heart rate, dry mouth, motor incoordination, and heaviness and tingling and/or numbness in the extremities, as well as facial flushing, urinary retention, and constipation (which follows early diarrhea).

Several very unpleasant side effects are, to a significant extent, dose-related. Doses of nutmeg greater than 15–20 grams can cause central nervous system excitation, agitation, frightening perceptual experiences, panicky feelings, delusions, pains in the chest and abdomen, abnormally rapid heartbeat, and parched mouth and throat. Very high doses can cause severe liver damage. Fatalities have resulted from overdose.

The duration of hallucinogenic effects is also dose-related; at typical doses it depends on the amount retained after vomiting. Therefore, effects may last from a few hours to 12 hours or more.

Unlike with most other hallucinogens, recovery from nutmeg intoxication is slow, and the user may experience alcohol-like hangover and severe muscle and bone aches for several days.

In North America, nutmeg is rarely the first-choice drug for hallucinogen users because of its undesired side effects and the slow period of recovery following nutmeg intoxication. Its use is generally restricted to prisoners and young teenagers. Therefore, its abuse potential is lower than that of other common hallucinogens in spite of its easy availability.

Opium

DRUG CLASS: NARCOTIC ANALGESIC

Opium is a crude resinous preparation obtained from the thick white exudate found in the unripe seed pods (capsules) of the opium poppy, *Papaver somniferum*, which grows in some areas of Europe, the Middle East, and Southern Asia. Opium is prepared by collecting the exudate from scored poppy pods and allowing it to dry in a shady area for several days. The crude opium gradually darkens in color to chestnut or darker brown and hardens to a tar-like texture; it has an unpleasant odor and a bitter taste that typically produces nausea. The dried substance is then shaped into lumps or bricks for sale or shipment.

Opium contains a number of naturally occurring alkaloids, including morphine, codeine, papaverine, thebaine, and narcotine. However, only morphine and codeine have psychoactive properties that attract abuse. Morphine comprises approximately 6%–12% (depending on source) of the bulk of crude opium, and codeine 0.5%–1.5%. Most of the total bulk, 75%–80% by weight, consists of a variety of substances which have little or no pharmacological activity.

Opium smokers increase the purity of the crude substance by boiling it in water until it forms an aqueous solution. The solution is then filtered, and the residue is boiled and filtered several times more so that the maximum opium yield can be extracted. On each occasion, the filtered solution is added to the original, and the final purified opium solution is once again boiled very slowly until only a black sticky paste (the purified opium) remains. The paste is then dried and smoked. Usually, the user lies down in order to lessen the impact of the nausea that smoking opium produces.

Opium smoking for its euphoric and sedative properties was once very widespread throughout the Middle East and Asia (particularly China); nowadays, the practice is much less frequently encountered and is largely confined to certain rural areas in that part of the world. During the latter half of the 19th century, opium smoking was widely encountered in some areas of North America and Europe, where the habit had been imported by Oriental laborers.

Opium has a dependence liability similar to that of morphine. However, crude opium is rarely found on the North American and European street drug markets. Morphine and heroin, being far less bulky, are much easier to smuggle.

Opium as an analgesic in clinical medicine has largely been replaced by naturally occurring, semisynthetic, and wholly synthetic substitutes (such as morphine, hydromorphone, and meperidine respectively). Nonetheless, a highly purified form of opium (with all of the inert bulk removed) is still occasionally used for any of the purposes for which morphine can be used. A product marketed under the trade name Pantapon is prepared for injection administration only; a standard dose contains the equivalent of approximately 10 mg of morphine. Paregoric is the generic name for a hydroalcoholic solution containing 4% tincture of opium as well as camphor, benzoic acid, and anise oil; doses of 5 or 10 ml (0.5 or 1.0 cl) of this solution correspond to 2 or 4 mg of morphine. Products containing paregoric as well as other nonpsychoactive drugs (e.g., Donnagel PG, Diban) are still widely used for control of diarrhea. Narcotic analgesic addicts often resort to paregoric products when other more potent drugs are not available.

Peyote

DRUG CLASS: HALLUCINOGEN

The small brownish-gray cactus *Lophophora williamsii* has been revered for centuries by a number of Indian tribes (including the Aztecs) in Mexico and the Southwestern United States. That part of the cactus of interest for its psychoactive properties is often called the mescal button. This is tufted with whitish "hair" and is green tipped. The button contains at least 15 pharmacologically active substances, the most important of which is the hallucinogen mescaline. Other alkaloids include a convulsant, a respiratory stimulant, and a reflex stimulant. It is generally agreed that mescaline taken in combination with the many other alkaloids in the peyote button produces more intense effects than mescaline taken alone. The typical amount taken is between three and six buttons.[1]

Traditionally, mescal buttons are dried until completely brown and then chewed and swallowed. However, since the taste is extremely bitter, modern hallucinogen users often grind the material into a powder and ingest it either in capsule form or in a solution of tea or fruit juice. Irrespective of the method by which it is taken, shortly thereafter severe nausea and vomiting ensue. Other early effects include dizziness, anxiety and sometimes panic, rapid and deep respiration, elevated heart rate and blood pressure, dilated pupils, chills, and profuse sweating.

Hallucinogenic effects tend to be experienced within one or two hours after ingestion. Ordinarily trivial objects in the environment seem to take on vivid characteristics. The user also experiences intense visual pseudohallucinations (i.e., known to the user to be unreal), often in geometric forms with strikingly brilliant colors.[2] Visual imagery predominates, although pseudohallucinations involving other sensory modalities (hearing, smell, taste) often accompany visual experiences and can also be intense. Synesthesia frequently occurs (i.e., the melding

[1] Indians may use substantially more in religious ceremonies.

[2] True hallucinations (i.e., hallucinations which the user believes truly represent reality) are less common.

of one sensory modality with another such that sounds are “felt” or music “seen”). Users also experience sensations of weightlessness, and distortions of time and space are common. There is a general feeling of detachment from worldly events, often accompanied by a prolonged exploration of the inner self. Some users report having experienced profound mystical revelations.

While the aforementioned are the desired effects, a few people experience frightening hallucinations and are terrified by their loss of contact with reality.

Tolerance develops rapidly to the main psychoactive agent of peyote, mescaline, within a few days of everyday use. Users must therefore abstain for a similar period in order to restore pretolerance sensitivity. Such a pattern of use reduces the likelihood of acquiring psychological dependence on peyote; physical dependence does not occur.

Peyote is used legally in the United States by Indians belonging to the Native American Church and is an integral part of their religious ceremonies. This group claims a membership of 250,000 in the United States and Canada, although many do not regularly partake in the peyote ritual. Peyote is rarely available in most areas of North America except for its careful distribution to congregations of the Native American Church. Its sacramental use has not been sanctioned in Canada.

Phenmetrazine

DRUG CLASS: CNS STIMULANT; ANOREXIANT

Phenmetrazine is a synthetic central nervous system (CNS) stimulant produced through chemical synthesis.[1] It occurs as a white odorless crystalline powder with a slightly bitter taste, very soluble in water and alcohol. In the past in Canada it was clinically employed as a diet pill for the short-term management of obesity arising from poor dietary habits. The maximum therapeutic daily dose was 75 mg taken orally in divided doses. Phenmetrazine produces a spectrum of CNS-stimulant effects almost identical to those produced by amphetamine, although the latter drug is more potent.

When phenmetrazine was originally introduced, it was promoted as a safe and nonaddictive alternative to the widely abused amphetamines. That claim, however, has proven to be incorrect. At higher dose levels (i.e., in excess of the therapeutically recommended dose) phenmetrazine can produce intense euphoria, particularly when injected intravenously, as well as heightened alertness, increased endurance, and increased self-confidence. For these reasons, it was widely abused in Europe and North America both orally by tablet and by intravenous injection. Abusers represented such divergent groups as athletes, students, housewives, long-haul truck drivers, and street drug consumers. The last group most commonly administered the drug by injection when more potent stimulants were not available; the other groups were mainly oral users. Some abusers had been known to take as much as 1,500 mg per day.

A principal toxic effect of phenmetrazine when taken at very high dose levels is a psychotic state virtually identical to amphetamine psychosis. This state is characterized by hallucinations, delusions, severe paranoia, and seemingly meaningless compulsive stereotyped behavior, and sometimes by bizarre or violent behavior. The psychosis may last up to several weeks even though no more of the drug is taken.

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[1] Phenmetrazine was formerly marketed in Canada (under the trade name Preludin), but it is no longer legally available. It is still available in the United States by prescription, although it is now classified under the Controlled Substances Act as a drug with a high abuse potential.

Tolerance develops rapidly to the anorexiant (appetite-suppressant) and other desired effects when phenmetrazine is regularly used; therefore, those users who wish to maintain the original intensity of effects must frequently increase the size of their daily dose. Regular use causes psychological dependence in many users, irrespective of the size of the daily dose taken. Psychological dependence is generally manifested as a persistent craving for the psychological effects, a preoccupation with procuring an adequate supply, and anxiety or even feelings of panic when the drug is not available. Chronic heavy use can also result in physical dependence. Abrupt abstinence by a physically dependent user typically causes exhaustion, lethargy, sleep disturbance, ravenous appetite, and emotional depression which may be severe.

The dependence liability of phenmetrazine is high, although not quite so high as that of amphetamine. Its actual abuse potential is now greatly reduced; it is no longer produced in Canada, and its production and medical use have markedly declined elsewhere.

Phentermine

DRUG CLASS: CNS STIMULANT;
ANOREXIANT

Phentermine (Ionamin) is a synthetic central nervous system (CNS) stimulant produced through chemical synthesis. It occurs as a white crystalline powder which is bitter to the taste and soluble in water and in alcohol. Phentermine is exclusively prescribed as a diet pill for the short-term management of obesity resulting from poor dietary habits. The therapeutic dose range is 15–30 mg taken orally in the form of a time-release capsule 10–14 hours before bedtime.[1] The effects produced are qualitatively identical to those produced by amphetamine, although the latter drug is significantly more potent. Common side effects of therapeutic doses of phentermine include increased heart rate and blood pressure, restlessness, insomnia, dry mouth, and diarrhea. Some users taking doses of phentermine higher than those therapeutically recommended can achieve euphoria, particularly when they administer the drug intravenously; the higher doses also produce increased alertness and endurance and enhanced feelings of self-confidence. Other users may experience unpleasant overstimulation, anxiety, agitation, dizziness, tremor, abnormally rapid heart rate, and abnormally high blood pressure. Very high doses (i.e., overdose) sometimes produce a toxic psychotic syndrome which may be manifested as hallucinations, confusion, delusional thinking, and assaultive behavior. Extreme overdose can result in severe cardiovascular irregularities, convulsions, and coma.

Tolerance to the anorexiant (appetite-suppressant) effect of this drug can develop as rapidly as within a few weeks with regular use. Regular high-dose abuse can result in the rapid acquisition of tolerance to its desired euphoric and CNS-stimulant actions. Thus, if users wish to maintain the original intensity of any of these desired effects, they must increase the size of their daily dose frequently. Chronic use/abuse of phentermine can produce a state of psychological dependence, characterized by a craving for the psychological effects produced by the drug, a preoccupation with obtaining an adequate supply, and

[1] E.g., a user who normally retires at 11 P.M. may take the drug at 9 A.M. The purpose of the timing is to ensure maximum daytime effects without interference with sleep.

anxiety or even feelings of panic if it is temporarily unavailable. Physical dependence seems to occur in chronic high-dose abusers; after abrupt abstinence, they experience such withdrawal symptoms as extreme fatigue and emotional depression.

The dependence liability of phentermine is fairly high, although not as high as that of amphetamine. It has recently been classified as a controlled drug in Canada because of mounting abuse; the greater difficulty in obtaining it has therefore reduced its abuse potential.

STP; DOM

DRUG CLASS: HALLUCINOGEN

Both STP and DOM have come to be used as designations for the same potent hallucinogenic compound—2,5-dimethoxy-4-methylamphetamine. This compound, produced by chemical synthesis, occurs as a tasteless, odorless, white crystalline powder. It is structurally related to MDA and amphetamine. "DOM" is an abbreviation of the chemical name. The origin of the street designation "STP," however, is uncertain. Some believe it is an abbreviation of "serenity, tranquility, and peace." Others suggest that it is taken from the widely used motor oil additive of the same name—perhaps a reference to its stimulant properties.

STP was virtually unknown, except (as DOM) to a few researchers, prior to its dramatic entry into the street-drug subculture in the summer of 1967. During a period of a few days, several thousand high-dose STP tablets were distributed in the San Francisco area, apparently free. The result was the admission of several users to local hospital emergency departments, all suffering a toxic psychosis which lasted up to four days after STP ingestion. Several of these patients who were treated with chlorpromazine, a powerful antipsychotic drug, experienced cardiovascular shock. Significantly, these drug effects differed substantially from those produced in research subjects by pure DOM followed by chlorpromazine. High doses of pure DOM (8 mg) did produce psychotic effects in some research subjects; however, these cleared within less than a day, and when the subjects were given chlorpromazine no significant adverse effects were observed. Therefore, researchers believe that the alleged STP substance distributed in 1967 was not pure DOM but rather a combination of a variety of drugs, one of which was DOM. The terms STP and DOM are now generally used interchangeably.

Small doses of pure DOM (1–2 mg) can produce mild euphoria, gregariousness, and pleasant central nervous system stimulation. Somewhat higher doses (e.g., 5 mg)[1] tend to produce mescaline- or LSD-like effects, including vivid visual imagery, intense perceptual distortions, pseudohallucinations (known to the user to be unreal), and feelings of dissociation from the environment. A number of unpleasant physical effects also occur. Most of these are experienced prior to the onset of hallucinogenic actions and include nausea and vomiting, dry mouth, shortness of breath, prickling or burning sensations on the skin, fatigue, tremors, muscle tension, increased reflex responses, and abnormal sensitivity to light. Other side effects include increased heart rate and blood pressure, pupillary dilation, increased body temperature, sweating, and loss of appetite. At such dose levels, hallucinogenic effects last for up to eight hours. Acute adverse reactions ("bad trips") to pure DOM include intense anxiety, panic, and occasionally psychotic reactions. "Bad trips" are more common with DOM than with most other hallucinogens.

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[1] Taken orally or by injection.

At higher dose levels, effects may last for up to 24 hours; they are generally more intense, and severe "bad trips" are frequent.

Tolerance can develop as rapidly as within three days to the subjective effects of pure DOM when it is taken on consecutive days. However, psychological and physical dependence are not known to occur. DOM has not become a popular hallucinogen, and its use in Canada is practically unknown. Its limited attraction is probably due to the duration and intensity of its effects and its reputation for producing "bad trips."

Strychnine

DRUG CLASS: CNS STIMULANT;
CONVULSANT;
POISON

Strychnine is a naturally occurring alkaloid which can be isolated from the dried ripe seeds of *Strychnos nux-vomica*, a small tree native to Indonesia, Malaysia, and other parts of the Orient. It can also be isolated from the seeds of the related plant *Strychnos ignatu* (St. Ignatius bean). The hydrochloride salt of strychnine is a white crystalline powder with a very bitter taste, slightly soluble in water and alcohol. In the past, it was widely used in "tonics," probably because of its reputation for stimulating the gastrointestinal tract and increasing voluntary muscle tone. However, these effects result only at unacceptably high doses.

Amendments to the Canadian Food and Drug Regulations in 1976 prohibit the inclusion of strychnine in any substance marketed for human use. It continues, however, to be used in rodent poisons.

Strychnine poisoning causes stiffening and twitching of the jaw, face, and neck muscles followed by increased reflex excitability such that even ordinarily very mild stimuli produce a violent muscle response. There are powerful thrusts of the lower limbs and later severe seizures in which the whole body may arch so rigidly that only the heels and head touch the ground. Between convulsions there may be several minutes of muscle relaxation.

Strychnine acts on certain areas of the brain and the spinal cord, where it appears to block normal inhibitory processes which control the voluntary muscles. Despite the extreme skeletal muscle disturbances, the higher brain centres of consciousness are not affected. Therefore, the victim consciously experiences these very painful muscle contractions, and without immediate therapeutic intervention can only apprehensively await the next severe spasm. Death results from paralysis of those brain centres in the medulla which control breathing. The paralysis is due to an oxygen deficit caused by several minutes of severely impaired respiration resulting from contraction of the diaphragm (i.e., asphyxiation). The fatal overdose range for adults is 50–100 mg, although some deaths have occurred at lower doses. As little as 15 mg can be lethal to children.

Treatment of strychnine poisoning has classically included intravenous injections of the short-acting barbiturates, although diazepam is now the drug of choice to combat the convulsions. Artificial support of respiration is also essential if breathing is impaired, as is removal of the patient from all avoidable sensory stimulation (light, sound, touch, etc.).

Folklore and some sensationalist journalism have suggested that LSD and other CNS stimulants such as amphetamines are sometimes adulterated with strychnine, supposedly for the purpose of enhancing their effects. Laboratory analyses of street drugs indicate that the practice is quite infrequent and the amounts of strychnine that do appear are very small.

TMA

(Trimethoxyamphetamine)

DRUG CLASS: HALLUCINOGEN

TMA (3,4,5-trimethoxyamphetamine) is a synthetic hallucinogen which usually appears as yellowish or beige powder. It is structurally related to both MDA and mescaline as well as to amphetamine. The typical hallucinogenic dose range is between 150 and 200 mg, taken orally or by injection. Lower doses (e.g., 50–100 mg) produce dizziness, lightheadedness, euphoria, garrulousness, and emotional disinhibition. Hallucinogenic doses produce effects similar to those of mescaline, including intense visual imagery, perceptual distortions, mainly visual pseudohallucinations (known to the user to be unreal), synesthesias (the melding of one sensory modality with another such that, e.g., music is "seen"), and dissociation from the environment. A number of amphetamine-like physiological effects occur prior to the onset of TMA's hallucinogenic actions; these can include behavioral arousal, slight motor incoordination, increased reflex responses, slight tremor, pupillary dilation, transient mild headache, and nausea and vomiting, as well as sweating, increased blood pressure and heart rate, loss of appetite, and increased respiratory rate.

Higher doses of TMA (300 mg or more) produce at least one effect which usually does not occur with higher doses of mescaline and related compounds: a tendency toward unprovoked antisocial behavior, manifested as anger or hostility toward others and, sometimes, grandiose beliefs about oneself.

There is insufficient information to characterize other adverse effects of this drug, and research has yet to be performed on tolerance and dependence issues. TMA does not appear to be used intentionally by those seeking hallucinogenic experiences. However, it has been often passed off on the street as MDA or some other psychoactive drug.

Section 5

Additional Drug Notes

Additional Drug Notes

Alphaprodine (Nisentil)—A synthetic narcotic analgesic with an analgesic potency approximately one-third that of morphine when equal doses by weight are injected subcutaneously. The duration of its effects is only one to two hours, somewhat briefer than that of other commonly used narcotic analgesics. The single therapeutic dose is 30–60 mg (administered by subcutaneous or intravenous injection).

Aminophylline (theophylline ethylenediamine)—A mildly potent CNS stimulant with important bronchodilator properties. It is clinically used for symptomatic treatment of bronchial asthma, chronic bronchitis, and similar conditions.

AMT (alphamethyltryptamine)—A synthetic hallucinogen with psychic effects similar to, although milder than, those of psilocybin. Other effects are more intense than with the latter drug, and AMT also has a longer duration of action, up to 16–18 hours.

Bromides (e.g., sodium bromide)—In the past used as sedative/hypnotics as well as anticonvulsants. Because of their toxic effects at higher doses and/or with chronic administration, bromides have been completely replaced for these uses by safer and more effective drugs.

Bufotenine—A hallucinogenic substance found in skin glands of certain toad species and in the mimosa plant, *Piptadina peregrina*, which grows in many areas of the West Indies and South America. Indians have used the plant for centuries in the form of a snuff which is widely called cohoba. Doses of 4–16 mg produce mescaline-like effects.

Calcium carbimide (Temposil)—A protective drug used in the treatment of alcoholism. Consumption of alcohol when calcium carbimide is present in the body can cause a violent and unpleasant reaction, similar to that produced by disulfiram (Antabuse). The therapeutic dose range is between 50 and 100 mg taken orally twice daily.

Cantharides (Spanish fly)—Falsely identified as an aphrodisiac, this substance is prepared from the crushed wings of the insect *Lytta vesicatoria*. It is extremely toxic: even very small amounts can cause severe burning sensations and blistering in the upper gastrointestinal tract and the genitals, as well as irreversible damage to the genitourinary tract and kidneys. Spanish fly has caused a number of deaths.

Catnip—An herb obtained from the plant *Nepeta cataria*, a member of the mint family. Catnip is known for producing playful behavior in cats. When smoked it can produce mild euphoria in humans, and for this reason is occasionally passed off to unsophisticated street buyers as marijuana.

Chlorphentermine (Pre-Sate)—An anorexiant (diet pill) used in the short-term management of obesity arising from poor dietary habits. The typical therapeutic dose is 65 mg (taken orally before breakfast). It is chemically related to amphetamine, and excessive use can produce tolerance and dependence.

Cyclazocine—A potent and long-acting narcotic antagonist which can precipitate withdrawal symptoms in narcotic-analgesic-dependent people. It can also rapidly reverse the effects of narcotic analgesic overdose. Cyclazocine is a powerful analgesic in its own right when narcotic analgesics are not present in the body. Chronic administration can cause physical dependence. Cyclazocine is not legally available in Canada.

DET (diethyltryptamine)—A synthetic hallucinogen chemically related to DMT. A hallucinogenic dose is approximately 50–60 mg. DET produces effects similar to those of DMT, although DET's effects last for a longer period of time (two to three hours).

Dextromoramide—A synthetic narcotic analgesic with an analgesic potency approximately twice as great as that of morphine when equal doses by weight are injected subcutaneously. This drug is not legally available in either Canada or the United States.

Dihydrocodeine—A semisynthetic narcotic analgesic derived from morphine with an analgesic potency approximately twice as great as that of codeine when equal doses by weight are injected subcutaneously. This drug is not legally available in Canada. Elsewhere it has been used both as an analgesic and as a cough suppressant.

Ethinamate (e.g., Valmid)—A synthetic sedative/hypnotic drug. Regular use results in tolerance to its desired effects. Chronic high-dose abuse can cause severe barbiturate-like dependence. Ethinamate is not available in Canada.

Ibogaine—A naturally occurring hallucinogenic alkaloid which is obtained from the roots of the West African plant *Tabernanthe iboga.* A hallucinogenic dose is approximately 300 mg, and its effects are similar to those produced by harmaline. Overdose may result in convulsions, paralysis, and death from respiratory arrest.

Isobutyl nitrite—A vasodilator (i.e., dilates blood vessels) which produces a spectrum of effects similar to amyl nitrite, although it is not specifically marketed for the treatment of any medical disorder. It is sometimes sold as an odorizer. It has been subject to some abuse for its intoxicating properties and its reputed ability to enhance sexual orgasm.

Kava-kava—A naturally occurring alkaloid obtained from the roots of the plant *Piper methysticum*, which grows on islands throughout the South Pacific. Small doses can produce mild euphoria; larger doses produce a more intense euphoria and perceptual distortions. Still larger doses cause a pleasant state of lethargy, usually followed by sleep. Chronic use can produce dependence and a number of adverse side effects.

Khat (or Qat)—A mild CNS stimulant obtained from the buds and leaves of the shrub *Catha edulis*, found in Yemen and many areas of Africa. Fresh khat leaves or buds can produce euphoria, pleasant stimulation, gregariousness, and sometimes hallucinations. Some users experience emotional depression, fatigue, and drowsiness when the effects of the drug wear off.

Laudanum—A hydroalcoholic solution containing 10% opium, widely used since the 16th century for a variety of maladies. It is now rarely employed.

Levorphanol (Levo-Dromoran)—A powerful synthetic narcotic analgesic with an analgesic potency approximately four times greater than morphine when equal doses by weight are injected subcutaneously. Levorphanol is reported to possess a very high dependence liability. The therapeutic dose range is between 2 and 4 mg twice daily (by injection).

Lidocaine (Xylocaine)—A synthetic local anesthetic employed in those surgical procedures for which cocaine could also be used. It is also used in a variety of topical anesthetic preparations. Lidocaine is not abused for its own sake, having no significant psychoactive properties other than causing drowsiness. However, because sniffing lidocaine produces a freezing sensation in the nasal passages (mimicking the initial effect of cocaine), traffickers often use it to dilute cocaine.

Mazindol (Sanorex)—An anorexiant (diet pill) used in the short-term management of obesity arising from poor dietary habits. Its effects are similar to, although milder than, those produced by amphetamine. The typical daily therapeutic dose is 2 mg taken orally one hour before lunchtime. This drug has been subject to abuse. Tolerance develops to mazindol's main effects, and chronic abuse can result in dependence.

Methysergide maleate (Sansert)—A semisynthetic drug used prophylactically for prevention of migraine and other forms of severe vascular headache. It is derived from an ergot alkaloid which is chemically related to LSD. The therapeutic dose is 2 mg three times daily (taken orally). Mild euphoria, feelings of unreality, and hallucinations sometimes occur at therapeutic dose levels, and these effects may be intensified at higher doses.

Metopon (methyldihydromorphinone)—A powerful semisynthetic narcotic analgesic derived from morphine. When administered by subcutaneous injection in equal doses by weight, metopon's analgesic potency is approximately three times greater than that of morphine. It is not legally available in Canada or the United States.

Nabilone—A synthetic analogue of tetrahydrocannabinol, which has been introduced recently in Canada for the treatment of the severe nausea and vomiting associated with certain types of anti-cancer therapy. An effective dose (2 mg) produces significantly less euphoria and heart rate abnormality than a comparable dose of THC.

Nalorphine—A potent narcotic antagonist which can precipitate withdrawal symptoms in narcotic-analgesic-dependent people and can also rapidly reverse the effects of narcotic analgesic overdose. Nalorphine can produce mild morphine-like effects when narcotic analgesics are not present in the body. It is not legally available in Canada.

Nitrazepam (Mogadon)—A member of the benzodiazepine family of drugs which has been recently introduced in Canada, nitrazepam is used for sleep induction as well as for control of certain types of seizures. The sleep-inducing dose range is 5–10 mg before bedtime (taken orally).

Noscapine (Noscatuss)—A natural alkaloid obtained from opium which exerts no analgesic, sedating, or euphoric effects. However, since it does suppress the cough reflex, it is employed for temporary relief of dry, irritating cough.

Oxymorphone (Numorphan)—A powerful semisynthetic narcotic analgesic derived from morphine, with an analgesic potency approximately 10 times greater than morphine when equal doses by weight are injected subcutaneously. Its degree of potency is greater than that of any other narcotic analgesic currently in use in either Canada or the United States. The single therapeutic dose range is 1.0–1.5 mg (administered by intramuscular or subcutaneous injection); when administered intravenously, the typical dose is 0.5 mg.

Paraldehyde—A sedative/hypnotic drug which has been used for sedation, induction of sleep, and treatment of alcohol withdrawal symptoms since the 19th century. However, it has a very disagreeable taste and odor, is irritating to tissues, and has a variety of other toxic effects. In recent years, it has been replaced by the barbiturates and other newer drugs.

PCE (cyclohexamine)—A synthetic dissociative anesthetic used in veterinary medicine. It is chemically related to phencyclidine (PCP) and produces a range of effects that are similar but seemingly more potent; hence its street name, "rocket fuel." PCE has been passed off as PCP, LSD, and other drugs. A few deaths have been attributed to PCE overdose.

Phenadoxone—A synthetic narcotic analgesic with an analgesic potency slightly less than that of morphine when equal doses by weight are injected subcutaneously. It cannot be regularly administered by needle because it produces marked irritation and pain at sites of injection. Phenadoxone is not legally available in Canada or the United States.

Phenazocine—A powerful synthetic narcotic analgesic with an analgesic potency approximately three times as great as that of morphine when equal doses by weight are injected subcutaneously. Phenazocine is not legally available in Canada.

Phendimetrazine—An anorexiant (diet pill) used in the short-term management of obesity arising from poor dietary habits. It produces effects similar to those of amphetamine, although it is not as potent. Chronic use can result in the acquisition of tolerance to its main effects and in dependence. Since it was widely abused, and since it offers no special therapeutic advantages over other products employed for the same purpose, phendimetrazine is no longer legally available in Canada.

Phenytoin (e.g., Dilantin)—An anticonvulsant drug which is effective in controlling grand mal and psychomotor seizures. It has no abuse potential, and unlike the barbiturates that are used to control seizures, it does not produce dependence. Tolerance to its antiseizure actions does not appear to develop. Most adult patients are maintained on 300–400 mg per day (taken orally in divided doses). Intravenous injection can be used in emergency situations.

Pholcodine—A powerful semisynthetic narcotic analgesic which has traditionally been used as an antitussive (cough suppressant). It is not legally available in Canada or the United States.

Reserpine (e.g., Serpasil)—A naturally occurring antipsychotic alkaloid obtained from the plant *Rauwolfia serpentina*. It has been used in India for centures in the treatment of a variety of maladies. In Western medicine, it has been employed in the treatment of psychosis and of hypertension (high blood pressure). Reserpine has been almost completely replaced in psychiatry by the phenothiazines and haloperidol.

Section 6

Trade Names

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Glossary of Medical/Scientific Terms

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Glossary of Street Drug Language

Trade Names of Single-Entity Prescription Products

Trade Name	*Nonproprietary*	*Article Title*
Amytal Sodium [+][o]	amobarbital sodium	Barbiturates
Antabuse [+][o]	disulfiram	Disulfiram
Apidex [o]	phentermine	Phentermine
Apo-Haloperidol [+]	haloperidol	Haloperidol
A-poxide [o]	chlordiazepoxide	Benzodiazepines I
Aquachloral [o]	chloral hydrate	Chloral Hydrate
Ativan [+][o]	lorazepam	Benzodiazepines I
Bacarate [o]	phendimetrazine	ADN[*]
Banobese [o]	phendimetrazine	ADN
Benzedrine [+][o]	amphetamine sulfate	Amphetamines
Biphetamine [o]	d-amphetamine (+ dl-amphetamine)	Amphetamines
Bontril PDM [o]	phendimetrazine	ADN
Butisol Sodium [+][o]	butabarbital sodium	Barbiturates
Carbolith [+]	lithium carbonate	Lithium Carbonate
Chloralvan [+]	chloral hydrate	Chloral Hydrate
Chlorprom [+]	chlorpromazine	Phenothiazines

[+] Marketed in Canada.
[o] Marketed in the United States.
[*] ADN—Additional Drug Notes, section 5.

Trade Name	*Nonproprietary*	*Article Title*
Chlor-Promanyl +	chlorpromazine	Phenothiazines
Corax +	chlordiazepoxide	Benzodiazepines I
C-Tran +	chlordiazepoxide	Benzodiazepines I
Dalmane + °	flurazepam	Benzodiazepines II
Darvon °	propoxyphene	Propoxyphene
Darvon-N + °	propoxyphene napsylate	Propoxyphene
Day-Barb +	butabarbital sodium	Barbiturates
Delcobese °	amphetamine	Amphetamines
Demer-Idine +	meperidine	Meperidine
Demerol + °	meperidine	Meperidine
Deprex +	amitriptyline	Tricyclic Antidepressants
Depronal-SA +	propoxyphene	Propoxyphene
Desoxyn °	methamphetamine	Amphetamines
Dexamyl + °	d-amphetamine (+ amobarbital)	Amphetamines
Dexedrine + °	d-amphetamine	Amphetamines
Dilantin + °	phenytoin	ADN
Dilaudid + °	hydromorphone	Hydromorphone
Dolophine °	methadone	Methadone
Doriden + °	glutethimide	Glutethimide
D-Tran +	diazepam	Benzodiazepines I
Elavil + °	amitriptyline	Tricyclic Antidepressants

Trade Name	*Nonproprietary*	*Article Title*
Endep °	amitriptyline	Tricyclic Antidepressants
E-Pam +	diazepam	Benzodiazepines I
Equanil + °	meprobamate	Meprobamate
Eskabarb + °	phenobarbital sodium	Barbiturates
Eskalith °	lithium carbonate	Lithium Carbonate
Fastin + °	phentermine	Phentermine
Felsules °	chloral hydrate	Chloral Hydrate
Fetamin °	methamphetamine	Amphetamines
Gardenal +	phenobarbital sodium	Barbiturates
Halcion +	triazolam	Benzodiazepines II
Haldol + °	haloperidol	Haloperidol
Hycodan + °	hydrocodone	Hydrocodone
Imavate °	imipramine	Tricyclic Antidepressants
Impril +	imipramine	Tricyclic Antidepressants
Ionamin + °	phentermine	Phentermine
Janimine °	imipramine	Tricyclic Antidepressants
Ketaject °	ketamine	Ketamine
Ketalar + °	ketamine	Ketamine
Largactil +	chlorpromazine	Phenothiazines
Levate +	amitriptyline	Tricyclic Antidepressants

Trade Name	*Nonproprietary*	*Article Title*
Levo-Dromoran + °	levorphanol	ADN
Librium + °	chlordiazepoxide	Benzodiazepines I
Lithane + °	lithium carbonate	Lithium Carbonate
Lithizine +	lithium carbonate	Lithium Carbonate
Lithonate °	lithium carbonate	Lithium Carbonate
Lithotabs °	lithium carbonate	Lithium Carbonate
Lomotil + °	diphenoxylate	Diphenoxylate
Lorfan + °	levallorphan	Levallorphan
Luminal + °	phenobarbital sodium	Barbiturates
Mandrax +	methaqualone (+ diphenhydramine)	Methaqualone
Medilium +	chlordiazepoxide	Benzodiazepines I
Meditran +	meprobamate	Meprobamate
Melfiat °	phendimetrazine	ADN
Mellaril + °	thioridazine	Phenothiazines
Meprospan-400 +	meprobamate	Meprobamate
Meravil +	amitriptyline	Tricyclic Antidepressants
Methidate +	methylphenidate	Methylphenidate
Meval +	diazepam	Benzodiazepines I
Miltown + °	meprobamate	Meprobamate
Modecata +	fluphenazine decanoate	Phenothiazines
Moditen Enanthate +	fluphenazine enanthate	Phenothiazines

Trade Name	*Nonproprietary*	*Article Title*
Moditen HCl +	fluphenazine hydrochloride	Phenothiazines
Mogadon +	nitrazepam	ADN
Narcan + °	naloxone	Naloxone
Nardil + °	phenelzine	Monoamine Oxidase Inhibitors
Nembutal + °	pentobarbital sodium	Barbiturates
Neo-Barb +	butabarbital sodium	Barbiturates
Neo-Calme +	diazepam	Benzodiazepines I
Neo-Tran +	meprobamate	Meprobamate
Nisentil + °	alphaprodine	ADN
Nobesine +	diethylpropion	Diethylpropion
Noctec + °	chloral hydrate	Chloral Hydrate
Noludar + °	methyprylon	Methyprylon
Novahistex DH +	hydrocodone (+ phenylephrine)	Hydrocodone
Nova-Pheno +	phenobarbital sodium	Barbiturates
Nova-Rectal +	pentobarbital sodium	Barbiturates
Novochlorhydrate +	chloral hydrate	Chloral Hydrate
Novodipam +	diazepam	Benzodiazepines I
Novoflupam +	flurazepam	Benzodiazepines I
Novoflurazine +	trifluoperazine	Phenothiazines
Novomepro +	meprobamate	Meprobamate

Trade Name	*Nonproprietary*	*Article Title*
Novopoxide +	chlordiazepoxide	Benzodiazepines I
Novopramine +	imipramine	Tricyclic Antidepressants
Novopropoxyn +	propoxyphene	Propoxyphene
Novoridazine +	thioridazine	Phenothiazines
Novotriptyn +	amitriptyline	Tricyclic Antidepressants
Numorphan + °	oxymorphone	ADN
Obetrol °	amphetamine	Amphetamines
Parest °	methaqualone	Methaqualone
Parnate + °	tranylcypromine	Monoamine Oxidase Inhibitors
Paveral +	codeine phosphate	Codeine
Pentogen +	pentobarbital sodium	Barbiturates
Pentothal + °	thiopental sodium	Barbiturates
Percodan + °	oxycodone (+ ASA and caffeine)	Oxycodone
Permitil °	fluphenazine	Phenothiazines
Phenazine +	perphenazine	Phenothiazines
Phendiet °	phendimetrazine	ADN
Phentercot °	phentermine	Phentermine
Placidyl + °	ethchlorvynol	Ethchlorvynol
Plegine °	phendimetrazine	ADN
Ponderal +	fenfluramine	Fenfluramine
Pondimin + °	fenfluramine	Fenfluramine

Trade Name	*Nonproprietary*	*Article Title*
Preludin °	phenmetrazine	Phenmetrazine
Presamine °	imipramine	Tricyclic Antidepressants
Pre-Sate + °	chlorphentermine	ADN
Pro-65 +	propoxyphene	Propoxyphene
Prolixin °	fluphenazine hydrochloride	Phenothiazines
Pronidin +	phentermine	Phentermine
Quāālude °	methaqualone	Methaqualone
Quietal +	meprobamate	Meprobamate
Regibon +	diethylpropion	Diethylpropion
Relaxil +	chlordiazepoxide	Benzodiazepines I
Reserfia +	reserpine	ADN
Reserpanca +	reserpine	ADN
Ritalin + °	methylphenidate	Methylphenidate
Rival +	diazepam	Benzodiazepines I
Robidone +	hydrocodone	Hydrocodone
Rouqualone-300 +	methaqualone	Methaqualone
Sanorex + °	mazindol	ADN
Sansert + °	methysergide bimaleate	ADN
Secogen +	secobarbital sodium	Barbiturates
Seconal + °	secobarbital sodium	Barbiturates
Seral +	secobarbital sodium	Barbiturates
Serax + °	oxazepam	Benzodiazepines I

Trade Name	*Nonproprietary*	*Article Title*
Serpasil + °	reserpine	ADN
Sinequan + °	doxepin	Tricyclic Antidepressants
SK-Bamate °	meprobamate	Meprobamate
SK-Chloral °	chloral hydrate	Chloral Hydrate
SK-Lygen °	chlordiazepoxide	Benzodiazepines I
SK-Phenobarbital °	phenobarbital	Barbiturates
SK-Pramine °	imipramine	Tricyclic Antidepressants
SK-65 °	propoxyphene	Propoxyphene
Solazine +	trifluoperazine	Phenothiazines
Solium +	chlordiazepoxide	Benzodiazepines I
Somnol +	flurazepam	Benzodiazepines II
Sopor °	methaqualone	Methaqualone
Statobex °	phendimetrazine	ADN
Stelazine + °	trifluoperazine	Phenothiazines
Stress-Pam +	diazepam	Benzodiazepines I
Supeudol +	oxycodone	Oxycodone
Talwin + °	pentazocine	Pentazocine
Temposil +	calcium carbimide	ADN
Tenuate + °	diethylpropion	Diethylpropion
Tepanil °	diethylpropion	Diethylpropion
Terfluzine +	trifluoperazine	Phenothiazines
Teronac +	mazindol	ADN
Thioril +	thioridazine	Phenothiazines

Trade Name	*Nonproprietary*	*Article Title*
Thorazine °	chlorpromazine	Phenothiazines
Tofranil + °	imipramine	Tricyclic Antidepressants
Tranxene + °	clorazepate dipotassium	Benzodiazepines I
Triador +	methaqualone	Methaqualone
Triflurin +	trifluoperazine	Phenothiazines
Trilafon + °	perphenazine	Phenothiazines
Trilium +	chlordiazepoxide	Benzodiazepines I
Trimstat °	phendimetrazine	ADN
Trimtabs °	phendimetrazine	ADN
Tualone-300 +	methaqualone	Methaqualone
Tuinal + °	amobarbital (+ secobarbital)	Barbiturates
Tussionex + °	hydrocodone (+ phenyltoloxamine)	Hydrocodone
Valium + °	diazepam	Benzodiazepines I
Valmid °	ethinamate	ADN
Vivol +	diazepam	Benzodiazepines I
Xylocaine + °	lidocaine	ADN
642 +	propoxyphene	Propoxyphene

Glossary of Medical/Scientific Terms

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abstinence
cessation of intake of a given drug following a period of protracted use.

acute
rapid; sudden; short-term; severe. *Cf.* chronic.

addiction, drug
a state of dependence upon a drug substance which is harmful to physical and/or mental health, social well-being, and/or economic functioning. *Syn.* drug dependence.

adjunct
supportive (as applied, e.g., to a therapeutic measure); a drug may be used as an adjunct to other ongoing treatment of a physical condition or psychological disorder.

alkaloid
a substance, chemically a base, found in plant material, including seeds; usually constitutes the active principle of the crude drug. Example: morphine.

allergy
hypersensitivity reaction to a specific substance.

alveoli
small air sacs of the lung.

amnesia
partial or total loss of recall of past events.

analgesic
a drug which can lessen pain without causing unconsciousness. Examples: ASA, narcotic analgesics.

analogue

pharmacologically, a drug different from another in structure, but similar in function; e.g., methaqualone is a barbiturate analogue.

anesthesia

pharmacologically, a drug-induced state characterized by complete loss of sensation in either part of or the whole body; may be accompanied by profound unconsciousness.

anorexia

marked loss of appetite; may be induced by drugs, by psychological problems, or by physical illness.

antagonist

pharmacologically, a drug which blocks or creates resistance to the effects of other drugs; e.g., naloxone is a narcotic antagonist.

anticholinergic

a drug which blocks the passage of impulses through certain autonomic nerves.

anticonvulsant

a drug which prevents or relieves seizures (convulsions). *Syn.* antiepileptic. Example: phenytoin (Dilantin).

antiemetic

a drug which controls or relieves nausea and vomiting. Example: phenothiazines.

anti-inflammatory

a drug which reduces tissue inflammation. Example: ASA.

antipyretic

a drug which reduces abnormally high body temperature/fever. Example: ASA.

antitussive

a drug which suppresses the cough reflex. Example: codeine.

asthma

an allergic condition characterized by wheezing, coughing, mucosal membrane secretion, and labored breathing.

ataxia
impaired ability to coordinate the voluntary muscles.

atrophy
the withering (wasting away) of a previously normal organ; may be caused by a number of factors including aging, disease, or toxic drug reaction.

autism
pathological preoccupation with oneself.

autonomic nervous system
that part of the nervous system which is not under voluntary or conscious control.

bradycardia (brachycardia)
abnormally slow heartbeat. *Cf.* tachycardia.

cardiac arrest
the complete cessation of heart activity.

cardiac arrhythmia
irregular beating of the heart.

cardiovascular system
the heart and blood vessels.

centiliter
100 milliliters, 0.1 liter.

central nervous system (CNS)
that part of the nervous system comprising the brain and the spinal cord.

cerebellum
that part of the brain which controls gross voluntary muscle coordination.

cerebrum
that part of the brain which controls higher nervous functions (e.g., thought, language).

chronic
of long duration. *Cf.* acute.

cirrhosis
the replacement of normal liver tissue with dysfunctional fibrous tissue. A progressive disease frequently associated with chronic alcoholism.

CNS
central nervous system.

coma
a state of profound unconsciousness from which the individual cannot be roused.

congener
pharmacologically, a drug which is chemically related to another.

convulsion
violent uncontrolled muscle spasm(s).

cross-dependence
the ability of a drug to suppress withdrawal in an individual physically dependent on another drug with similar pharmacological effects; narcotic analgesics, e.g., share cross-dependence, as do many sedative/hypnotics.

cross-tolerance
a bodily condition of reduced sensitivity to the effects of a drug due to the acquired tolerance to another drug which produces similar pharmacological effects; narcotic analgesics, e.g., share cross-tolerance.

cyanosis
bluish color in the skin and mucous membrane caused by insufficient oxygen in the blood and/or markedly insufficient blood in the capillaries.

delirium tremens (DTs)
a protracted phase of alcoholic withdrawal characterized by frightening hallucinations, delusional thinking, extreme mental

confusion, disorientation, severe agitation, and abnormally high body temperature.

delusion

a false but fixed belief (or set of beliefs) which an individual adamantly insists is true irrespective of evidence to the contrary; types of delusion include (1) delusions of persecution—beliefs that specific others wish to harm one; (2) delusions of grandeur—beliefs of extreme self-importance or of extraordinary ability, or total identification with an important historical figure; (3) delusions of reference—beliefs based on incorrect assumptions that unrelated events or the behavior of others specifically relates to oneself.

dependence, drug

a state of dependence upon a drug substance which is harmful to physical and/or mental health, social well-being, and/or economic functioning.

dependence liability

the relative propensity of a drug to create dependence in the user.

depressant

a drug which causes the functions of an organ system to slow down; e.g., barbiturates act as depressants on the central nervous system.

depression

(1) an effect on an organ system of the body in which the functions of that system are slowed down;
(2) an emotional state (or mood) characterized by feelings of despair and unhappiness; may be normal or abnormal depending on its cause, severity, and chronicity.

derivative

a substance derived from another substance by chemical manipulation; e.g., heroin is derived from morphine by exposure of morphine to acetic anhydride.

detoxication

removal of or neutralizing of toxic (harmful) drug effects.

diffuse
to spread evenly across a surface.

disinhibition
reduction or loss of inhibition; e.g., emotional disinhibition results in greater freedom of emotional expression.

disinhibitor
pharmacologically, a drug which facilitates the loss of inhibitions; e.g., alcohol is an emotional disinhibitor.

dissociative agent
a drug which produces feelings of dissociation or remoteness from the environment (e.g., PCP).

diuretic
a drug with the specfic property of inducing urine flow.

drug
any chemical substance which is used for its physiological or psychological effects.

dysphoria
an unpleasant emotional state, such as anxiety or depression. *Cf.* euphoria.

dysfunction
abnormal or impaired function.

EEG (electroencephalograph)
electrophysiological recordings of brain activity, obtained from electrodes attached to various areas of the scalp; often used in sleep research and to assist in detecting and diagnosing brain disorders.

endogenous
originating within the body. *Cf.* exogenous.

euphoria
a highly exaggerated feeling of well-being. *Cf.* dysphoria.

euphoriant
a drug which produces euphoria.

exacerbation
intensification; making worse.

exogenous
originating outside of the body; i.e., related to external events. *Cf.* endogenous.

gram (g)
1,000 milligrams; approximately 28 grams equal one ounce and 454 grams equal one pound.

grand mal seizure
a generalized seizure.

half-life
pharmacologically, the time required for half the amount of a drug in the body to be eliminated or converted into another substance.

hallucination
a false subjective perception believed by the individual to be real; may involve any of the senses; may be induced by drugs, psychological disorder, brain damage, or physical illness. *Cf.* pseudohallucination.

hazardous
presenting a heightened probability of harm or injury.

hemorrhage
escape of blood from blood vessel(s).

hepatitis
inflammation of the liver, caused usually, but not always, by viral infection; a form of hepatitis can be caused by chronic exposure to toxic substances such as alcohol.

hyperreflexia
exaggerated reflex response to one or more stimuli.

hypersensitivity
abnormal sensitivity; hypersensitivity reaction is an extreme reaction to a stimulus, such as to a drug.

hypertension
abnormally high blood pressure. *Cf.* hypotension.

hypertensive crisis
severely elevated blood pressure.

hyperthermia
abnormally high body temperature. *Syn.* hyperpyrexia. *Cf.* hypothermia.

hypotension
abnormally low blood pressure. *Cf.* hypertension.

hypothermia
abnormally low body termperature. *Cf.* hyperthermia.

hypnotic
a drug which induces sleep. Examples: barbiturates, methaqualone.

iatrogenic
resulting from erroneous treatment by a physician, or essential treatment with associated risk, that produces a pathological state in the patient.

illusion
a distortion or misrepresentation of external reality believed by the individual to be an accurate representation; may involve any of the senses. *Cf.* pseudoillusion.

inhibitor
a drug substance which blocks certain physiological actions; e.g., a monoamine oxidase (MAO) inhibitor blocks the metabolism of monoamines.

intoxication
(1) inebriation;
(2) a state of poisoning.

intramuscular
within a muscle.

intravenous
within a vein.

kilogram (kg)
1,000 grams; 2.2 pounds.

lethality
capacity to kill.

libido
life force; usually in reference to sexual drive.

liter
1,000 milliters; 0.88 Imperial quart or 1.057 U.S. quarts.

manic-depressive psychosis
a psychotic disorder characterized by episodic extreme mood swings.

metabolism
pharmacologically, a process whereby drug substances are converted in the body into different substances (metabolites).

microgram (μg)
0.001 milligram; 1,000 micrograms equal one milligram.

milligram (mg)
0.001 gram; 1,000 milligrams equal one gram.

milliliter (ml)
0.001 liter; 1000 milliliters equal one liter.

narcotic
literally, that which benumbs or deadens. The term is used by

many scientists and practitioners to encompass all those drugs which in this book are referred to as narcotic analgesics (i.e., opiates and opioids). "Narcotic" has a different meaning in the criminal satutes of some countries. In the laws of Canada, for example, narcotics include such drugs as cannabis and cocaine.

opiate
a naturally occurring (e.g., morphine) or semisynthetic (e.g., heroin) narcotic analgesic originating from the opium poppy, *Papaver somniferum*. *Cf.* opioid.

opioid
(1) a wholly synthetic narcotic analgesic which mimics the actions of the naturally occurring opiates (e.g., methadone, meperidine);
(2) a generic term used by some pharmacologists to encompass all synthetic, semisynthetic, and naturally occurring narcotic analgesics.

overdose
any dose in excess of that therapeutically indicated.

palpitation
rapid and forcible pulsation of the heart.

paranoia
a condition of abnormal suspiciousness.

paradoxical reaction
a reaction to a drug which is the opposite of the anticipated effect.

parenteral
by injection.

Parkinson's disease, parkinsonism
a brain disorder characterized by involuntary tremors, muscle twitches, and peculiar gait.

pathology
the study of disease.

peripheral neuropathy

disease or damage to nervous tissue other than the brain and spinal cord.

polyneuropathy

a disease condition involving several nerves.

premorbid

preceding a disease state or psychological disorder.

pseudohallucination

a hallucination known to the individual to be unreal. *Cf.* hallucination.

pseudoillusion

an illusion known to the individual to be unreal. *Cf.* illusion.

psychoactive drug

any drug which affects emotions, thoughts, and/or behavior.

psychomotor

concerning voluntary muscular movement.

psychopathology

the study of psychological disorders.

psychopharmacology

the study of the effects of drugs on perception, thought, emotions, and behavior.

psychosis

a major mental disorder which greatly interferes with an individual's ability to function in society.Significant impairment of thought, judgment, and ability to interpret reality and emotions, as well as impairment of ability to communicate and of ability to behave appropriately, is experienced. One may further suffer delusions, hallucinations, memory loss, poor impulse control, and behavioral regression. Psychosis may be of emotional origin or caused by brain damage, disease, nutritional deficiency, hormonal imbalance, or aging, as well as by a variety of drugs and nondrug substances. *See* manic-depressive psychosis; schizophrenia; toxic psychosis.

psychotomimetic
pharmacologically, a drug which can cause in users psychological reactions which mimic natural forms of psychosis. *Syn.* psychotogenic.

psychotropic drug
(usual meaning) psychotherapeutic drug.

receptor sites (target sites)
specific sites in the body with which a drug interacts in order to produce its effects.

recidivism
the tendency to repeat past socially unacceptable behavior.

REM (rapid eye movement) sleep
a recurring phase of normal sleep characterized by constant oscillation of the eyeballs underneath the eyelids, continuous dreaming, and deep voluntary-muscle relaxation.

respiratory arrest
cessation of breathing.

schizophrenia
a psychotic disorder characterized by severe disturbances of thought, mood, and behavior; behavior is regressive and bizarre, and delusions and hallucinations are often (but not always) manifested.

sedation
a state of quiescence and relaxation.

seizure
a pattern of abnormal rhythmic electrical activity in the brain and its sequelae. The manifestations can be motor (i.e., as in convulsions), sensory, autonomic, or psychic.

side effect
a drug-induced effect which accompanies the effect(s) for which a given drug is taken.

skeletal muscle
elongated muscle tissue attached to skeletal structures and under voluntary control.

smooth muscle
muscle tissue found in visceral structures (e.g., heart, stomach) and not under voluntary control.

solvent
any substance which is able to dissolve other substances.

soporific
sleep-inducing.

subcutaneous
beneath the skin.

status epilepticus
persistent and severe seizure activity with little or no interruption.

stupor
extreme lethargy; partial or nearly complete unconsciousness.

syncope
fainting; syncope results from a sudden drop in blood pressure.

synesthesia
the melding of one sensory modality with another such that, e.g., music is "seen." Many hallucinogenic substances produce synesthesia.

tachycardia
abnormally rapid heartbeat. *Cf.* bradycardia.

tachyphylaxis
a form of complete tolerance which develops rapidly to certain drugs (e.g., to many hallucinogens) either during the course of

acute intoxication or when they are used every day; it is a state in which no additional doses of the drug will produce any effect until sensitivity is restored by a period of abstinence. *Cf.* tolerance. Cross-tachyphylaxis refers to the same sensitivity applying to certain other drugs which produce similar effects. *Cf.* cross-tolerance.

tolerance

reduced sensitivity to a drug resulting from the adaptation of the body to repeated exposure to that drug; thus, higher doses become necessary in order to maintain the original response to the effects.

toxic psychosis

psychotic state caused by drugs or other foreign agents (e.g., lead); normally disappears when the psychosis-inducing substance is eliminated from the body. *See* psychosis.

toxicity

(1) a state of being poisoned;
(2) adverse effects created by a drug.

ulcer

a lesion on the skin or on any mucosal surface in the body.

vasoconstriction

constriction of the blood vessels.

vasodilation

dilation of the blood vessels.

withdrawal sickness

the aggregate of physical and psychological symptoms created in individuals by abstinence from a drug upon which they are physically dependent. *Syn.* abstinence syndrome, withdrawal reaction.

Glossary of Street Drug Language

The colorful terminology which comprises street drug language is derived from the attributes or characteristics of the drugs, of drug-related activities, of users, etc. In most instances, knowing the particular attributes of a drug (e.g., its actions, appearance) or the characteristics of a user (e.g., type of drug used, pattern of use) is sufficient to permit an understanding of the applied term. Methamphetamine, for example, is commonly called "speed," an obvious reference to the intensity of its stimulating effects. Users are often called "speeders." And the derogatory term "speed freak" is applied to the heavily dependent users whose behavior is often unpredictable, erractic, and sometimes bizarre. "Ripped" and "wrecked" graphically describe the exhausted condition of a methamphetamine user after several consecutive days of heavy use.

Many street terms move into general use through frequent public exposure in the media and through their use by popular personalities such as entertainers. The term "pusher," for example, brings to mind one who sells drugs illicitly, and it is the most widely accepted term, as is "junkie" for a heroin addict and "cold turkey" for abrupt drug withdrawal.

Street drug language is constantly changing. New terms come rapidly into vogue. Others become obsolete just as rapidly, and still others which had fallen into disuse can return to popularity.

GLOSSARY

Acapulco gold
a particularly potent form of marijuana grown in the Acapulco (Mexico) area. *Syn.* gold leaf. *See also* gold.

acid
LSD (d-lysergic acid diethylamide). *Syn.* blue cheer, cubes, lids, wedges.

acid freak
See head. *Syn.* acid head.

ack-ack
Method by which heroin is smoked on the tip of a burning cigarette.

alley juice
very cheap wine; isopropyl alcohol (which is also sometimes consumed by skid row alcoholics).

amped
high on amphetamines. *See also* overamped.

angel dust
(1) phencyclidine (PCP);
(2) PCP sprinkled on marijuana in powdered form and smoked. *Syn.* supergrass.

babysitter
See copilot.

back-up
a procedure permitting blood to back into a syringe to ensure that the needle is in a vein (a frequent precaution taken by veteran heroin addicts).

bad trip
an unpleasant, frightening, or even terrifying experience occurring after the ingestion of a hallucinogenic drug (e.g., LSD) or after the ingestion of other drugs with hallucinogenic properties (e.g., PCP). *Syn.* bummer, bum trip.

bag
a unit of drug purchase—from the small translucent envelope or folded paper usually containing highly diluted street heroin, possibly as low as 1%–3% pure. "Nickel" bags ($5.00) and "dime" bags ($10.00) describe prices which have long since substantially increased.

bang
See rush.

barbs
barbiturates. *Syn.* goofballs, downers, sleepers.

bayonet
hypodermic syringe.

beautiful
describing a drug of an unusually good quality, producing exceptionally intense euphoria ("The stuff is beautiful").

belt
(1) "high" or euphoria produced by a drug;
(2) a large mouthful of alcohol;
(3) to rapidly consume alcohol ("He belted down the whole bottle").

belt padding
increasing the dosage of a drug to compensate for acquired tolerance.

bennies
Benzedrine pills (amphetamine sulfate).

big "C"
cocaine.

binge
usually refers to a sustained period (i.e., several days) of uninterrupted heavy alcohol consumption; occasionally refers to the same practice with other drugs.

black beauties
Biphetamine capsules (combined d- and dl-amphetamine; not legally available in Canada).

black jack
paregoric cooked to concentrated form and injected; used mainly when other narcotics are unavailable.

blackout
amnesia for events occurring while heavily intoxicated with alcohol or other sedative/hypnotic drugs.

blast
See rush.

blotter
paper on which LSD has been absorbed so that it can escape detection.

blow
to sniff or snort; nasal inhalation; also inhalation of smoke ("blowing grass").

blow your mind (or mind-blowing)
referring to extraordinarily thrilling or exciting experience and usually subjectively favorable ("This stuff will blow your mind").

Blue Cheer
a combination of LSD, methamphetamine, and strychnine.

blue velvet
paregoric plus tripelennamine (an antihistamine) crushed and combined in solution for needle administration, producing an intense euphoric high. *See reference in* Pentazocine *article.*

blues
Amytal sodium capsules. *Syn.* blue heavens, blue birds. *See* Barbiturates *article.* (Not to be confused with Heavenly Blues, a variety of morning glory.)

bombed
high or intoxicated on alcohol or other drugs.

bombita
heroin and cocaine combined. *Syn.* dynamite, speedball.

boost
to shoplift.

bread
money.

brick
(from shape) compressed block of opium, morphine, or hashish, usually a kilogram.

bring down
(1) to precipitate a "crash" from the excessive agitation produced by stimulants, via the ingestion of CNS depressants (usually barbiturates or similar drugs);
(2) to help reduce highly adverse effects produced in some hallucinogen users via talk, reassurance, and (sometimes) minor tranquillizers. *Syn.* talk down.

bring it up
to dilate a vein prior to injection.

brody, to throw a
to feign illness or withdrawal in an attempt to obtain a narcotic prescription from a sympathetic physician.

bummer
(1) *See* bad trip;
(2) a bad or unpleasant experience not necessarily related to drug use.

burned out
in a state of brain or chronic behavioral impairment resulting from chronic heavy drug use.

bum rap
arrest for a crime one did not commit.

burned
cheated by a pusher through misrepresentation of the true identity, quantity, and/or purity of the purchased drug..

businessman's lunch
DMT, a hallucinogen with potent effects lasting 30–60 minutes. *See* DMT *article*.

bust
arrest by authorities and confiscation of a quantity of illicit drugs ("There was a bust last night," "He was busted last night").

button
peyote button. *See* Peyote *article.*

buy
a purchase, usually in reference heroin ("She made a buy").

buzz
a moderately pleasurable high.

cactus
from peyote cactus. *See* Peyote *article.*

candy
cocaine.

cap
capsule containing drugs in granule, crystal, liquid, or powdered form.

channel
vein used for injecting drugs.

charge
See rush.

charged up
See amped.

chemicals
synthetic drugs (e.g., amphetamines, LSD).

chippying (or chipping)
taking narcotic analgesics on an occasional or irregular basis, not sufficiently often to become physically dependent. *Syn.* weekend habit.

Christmas trees

Dexamyl tablets (green, triangular, and scored down the middle), a combination of dextroamphetamine and amobarbital.

clean

drug free ("I've been clean for over three years"). *Syn.* straight.

clean up one's act

to quit using drugs.

coast

See nod.

coke

cocaine.

cold turkey

abrupt withdrawal from a physically addicting drug through total abstinence, used most commonly in reference to heroin withdrawal. The derivation is though to be related to the highly prominent gooseflesh during heroin (or other narcotic analgesic) withdrawal, giving the appearance of a plucked turkey. *Syn.* kicking the habit.

collar

to arrest ("He's been collared three times").

Colombian red

potent strain of marijuana, its name designating its area of origin (Colombia) and its hue.

come down

to experience the gradual wearing-off of the effects of a drug after achieving a "high."

connection

(1) pusher;
(2) middle man between street pusher and higher-level drug source;
(3) in the plural, refers to the complex network from local producer (or grower) to street user.

contact high

mild euphoria occurring in non-smokers and believed by them to be the result of inhalation of the marijuana fumes produced by smokers. Actually, the individual's mental set and positive response to the elevated mood of the smokers are probably the most significant contributors.

cook

to dissolve powdered narcotics or other drugs in preparation for injection by mixing with water and heating the solution in a spoon or similar object over a flame.

cop

to purchase drugs ("They copped a lid of grass"). *Syn.* buy.

copilot

(1) an individual knowledgeable about the effects of hallucinogens, particularly in the case of LSD, who provides reassurance and reality contact for the neophyte user. *Syn.* babysitter, guide;
(2) amphetamine.

cotton

a small amount of cotton batting used to filter impurities from dissolved heroin as it is drawn into the hypodermic.

cotton, asking for

refers to an impoverished heroin addict unable to afford a "buy" scrounging the cotton used as a filter by other addicts so that a very weak heroin solution can be made. *Syn.* cotton picker.

crash

the pronounced and often rapid transition, produced by abrupt abstinence from amphetamines, cocaine, or other stimulants, from a state of CNS overstimulation to a state of CNS depression, initially characterized by prolonged sleep and followed by psychic depression and extreme hunger. Sometimes it is purposely precipitated by administration of barbiturates or similar drugs. (Not to be confused with "coming down," which connotes a less dramatic transition.)

crater

a deep flesh indentation at a particular site which has been subjected to repeated intravenous injections.

croaker

(outmoded) a doctor known to addicts as willing to prescribe narcotics freely.

crystal

methamphetamine. *Syn.* speed.

cube

a sugar cube containing LSD, a convenient form in which to ingest the minute quantity of the substance required to produce hallucinogenic effects.

cut

to adulterate or dilute. *Syn.* shave.

daily fix

methadone dispensed once daily in maintenance programs.

deal

to sell drugs. *Syn.* push.

dealer

one who sells drugs. *Syn.* pusher.

dexies

Dexedrine (dextroamphetamine sulfate).

dig

(1) to enjoy (“He digs smoking grass”);
(2) to understand (“I dig what you mean”).

dillies

Dilaudid (hydromorphone).

dolly

Dolophine (methadone); also used to refer to methadone generally.

dope

in earlier reference, heroin specifically (from its effect on the user); now a general term for many drugs of abuse.

dot

a dose of LSD so small that it is difficult to see with the naked eye (50–75 micrograms).

downer

(1) broadly used to refer to barbiturates, tranquillizers, and other drugs which produce sedation and/or sleep;
(2) an event which is depressing.

dragged

a mild anxiety and fatigue state sometimes following marijuana intoxication.

dreamers

narcotic analgesic drugs.

drop

to ingest a pill, tablet, or capsule orally. Most closely identified with LSD ("to drop acid").

dry

state of abstinence for an alcoholic

dry out

to abstain from drugs or alcohol after prolonged use to the point of substantial or complete loss of tolerance.

dry up

refers to the situation when illicit drugs, usually heroin or other narcotic analgesics, are not available at any cost—for example, when the authorities intercept usual supplies. When the street "dries up," panic often ensues among physically dependent users. Pharmacy thefts tend to peak at such times.

dust

(1) a drug in powder form;
(2) cocaine;
(3) PCP.

dusting

combining marijuana and heroin and rolling it in a form to be smoked.

eater

(outmoded) one who engages in the practice of ingesting opium orally.

echoes

LSD flashbacks which persist for an extended period of time after using the drug.

eighth

a measure of drug by weight as a fraction of an ounce (one-eighth); similarly, a "sixteenth" is one-sixteenth of an ounce, and so on.

elephant

phencyclidine (PCP). *Syn.* hog, angel dust.

eye opener

the first heroin (or other narcotic analgesic) injection of the day, without which withdrawal may rapidly ensue. *Syn.* morning shot.

factory

a location where illicit drugs are synthesized or otherwise processed for street sale. *Syn.* underground factory, basement laboratory.

far out

(1) exciting or thrilling;
(2) strange or peculiar.

fiend

outmoded term for compulsive drug user ("dope fiend").

fit

paraphernalia for injecting drugs. *Syn.* kit, works.

fix

a quantity of drugs, usually heroin, necessary to satisfy the immediate needs of a physically dependent user.

flake	cocaine. *Syn.* Big C, snow, coke.
flaky	(from flake) acting a bit crazy or strange.
flash	*See* rush.
flashing	inhaling glue or other products containing solvents.
flip out	to experience a severe, but temporary, psychological reaction to a drug, including psychotic symptoms. *Syn.* freak out.
floating	intoxicated, usually in reference to drugs other than alcohol. *Syn.* high, stoned, flying.
flow	to "give in" to the psychic effects of a drug rather than fight them.
flying	*See* floating.
Flying Saucers	trade name for a variety of morning glory seed with hallucinogenic properties.
freak	(1) one who behaves in a bizarre manner; (2) one who chronically uses large amounts of a specific drug (e.g., "acid freak," "speed freak").
freak out	*See* flip out.
freeze	a situation of unavailability of drugs, usually in reference to heroin ("A freeze is on").

front
(1) to acquire drugs when payment is to be made by a reliable third party known to the seller;
(2) to purchase drugs on short-term credit.

fruit salad
a reckless combination of drugs.

gap
to yawn (one of the earliest symptoms of heroin withdrawal).

garbage
See junk.

garbage head
indiscriminate polydrug user.

gee gee
opium pipe.

get off
to quit using drugs.

get off on
to be thrilled or exhilarated by something ("I get off on speed"). *Syn.* turn on.

get on
to begin to use drugs; to take drugs for the first time.

get it on
(1) to begin the first drug episode of the day;
(2) to achieve a floating or high feeling.

glass eyes
narcotic analgesics addict, who often has a glassy stare after having "hit up."

God's drug (God's own medicine)
morphine (a reference to its natural rather than synthetic origins).

More recently the term has also been used with regard to the practice of using marijuana as a sacrament in certain religious cults.

going down
going on, happening ("What's going down?").

gold
formerly certain specific strains of marijuana owing to their color; now adopted generally to refer to particularly potent marijuana.

goods
drugs, usually narcotic analgesics, to be bought and sold ("Have you got the goods?").

goofball
barbiturate. *Syn.* barbs, sleepers, downers.

grapes
cheap wine. *Syn.* alley juice.

grass
marijuana. *Syn.* pot, weed, etc.

grooving
(generally outmoded) under the influence of narcotic analgesics.

guide
See copilot (1).

H
heroin.

habit
the state of physical dependence, usually on narcotic analgesics.

hammer coming down
the rapid and dramatic transition from a normal feeling state to that which results from the full impact of a drug, usually in reference to the effects of a drug intravenously administered.

hard drugs
narcotic analgesics; also used to cover any drug which is controlled by federal narcotics statutes, such as cannabis or cocaine (even though cannabis is usually referred to as a "soft" drug because of the relative mildness of its effects and its low dependence liability).

hash
hashish.

hash oil
See honey oil.

head
a heavy regular user of a drug. Reference is often made to the specific drug, such as "acid head."

hearts
Dexedrine tablets (5 mg, pale orange, triangular).

heaves
violent retching and vomiting occurring during narcotic analgesic withdrawal.

Heavenly Blue
trade name for a morning glory seed which has hallucinogenic properties.

hot shot
an unusually pure dose of heroin (which can produce dangerous effects in users tolerant to only weak street heroin).

high
drug-induced euphoria.

hit
injection of drugs.

hog
phencyclidine (PCP). *Syn.* elephant, angel dust.

honey oil (hash oil)
highly purified oil of hashish, which has the highest concentration of THC among cannabis-derived products.

hooked
physically dependent on a drug (usually referring to a narcotic analgesic, such as heroin).

horse
heroin.

housewives' disease
dependence on minor tranquillizers.

hunting
desperate drug-seeking just prior to and at onset of withdrawal.

hustling
the heroin addict's daily routine of illegal activities in order to obtain sufficient money to buy more heroin.

hype
(1) something which produces intense excitement and interest ("That stuff's a hype");
(2) to be intensely excited and interested ("She's really got me hyped").

into
engaging in habitual use of a drug or variety of drugs ("She's into downers").

J
marijuana cigarette. *Syn.* joint.

jag
(1) the state of being under the influence of solvents ("He's on a glue jag");
(2) (outmoded) the state of being under the influence of amphetamines.

joint
marijuana cigarette. *Syn.* J.

jolt
See rush.

juice
cheap wine; more recently, liquid preparations of narcotic analgesic cough suppressants (e.g., hydrocodone, hydromorphone).

junk
diluted heroin.

junkie
heroin addict.

kicking the habit
abruptly abstaining from a physically addicting drug, used most commonly in reference to heroin. The derivation is thought to be related to the uncontrollable spasmodic jerking and kicking occurring during the peak period of heroin withdrawal. *Syn.* going cold turkey. The term may also refer more generally to overcoming any drug habit.

kilo
kilogram. *Syn.* K, ki, kee, key.

kit
paraphernalia for injecting drugs. *Syn.* fit.

knockout drops
liquid chloral hydrate, or chloral hydrate plus alcohol. *Syn.* Mickey Finn.

lace
(1) purposely to add one drug to another in order to produce a different or more potent effect (e.g., marijuana laced with powdered PCP);
(2) to dilute a drug with nonpsychoactive adulterants—often

without the buyer's knowledge (e.g., heroin laced with quinine). *Syn.* cut.

laughing gas
nitrous oxide.

leaf
marijuana. *Syn.* grass, pot, weed, smoke, etc.

leapers
amphetamines.

legal high
a high produced by legally available substances (other than alcohol) not requiring a prescription, such as certain solvents, herbs (e.g., dill), spices (e.g., nutmeg), and over-the-counter preparations containing codeine.

lid
a quantity of marijuana for street sale, approximately one ounce.

lid poppers
amphetamines.

line
a unit dose of cocaine, approximately 1/30 gram.

lines
See tracks (1).

loads
codeine plus glutethimide (Doriden).

loaded
drunk or heavily intoxicated.

loco weed
marijuana. *Syn.* grass, leaf, weed, pot, etc.

love drug
MDA; also, methaqualone.

"Lucy in the Sky with Diamonds"
popular Beatles song, which many imagined to be a direct reference to the effects of LSD.

ludes
Quāālude (methaqualone).

lush
heavy drinker or alcoholic.

magic mushroom
usually refers to psilocybin, but has also been used to refer to other hallucinogenic mushrooms. *Syn.* sacred mushroom.

mainline
to inject intravenously. Popular term with heroin and amphetamine users. *Syn.* shoot up.

Mary Jane or maryjane
marijuana. *Syn.* grass, loco weed, leaf, pot, smoke, etc.

mesc
mescaline

meth
(1) methamphetamine. *Syn.* speed;
(2) methadone.

Mexican
marijuana grown in Mexico. Mexican brown and Mexican green are specific grades, the former being the more potent.

Mickey Finn
chloral hydrate. *Syn.* knockout drops.

mike
a microgram (one-millionth of a gram), a common measure for LSD, a typical dose of which is 50–100 micrograms.

milk
(from milk sugar) crystals of lactose frequently used in diluting heroin, so called because of the similarity in appearance.

mind-bending
referring to the experience produced by a hallucinogenic drug.

mind-blowing
referring to a drug that produces an extraordinarily powerful reaction, usually a favorable experience ("Those uppers blew my mind").

Miss Emma
morphine. *Syn.* M, morph, soldier's drug.

monkey
(outmoded) the state of being in withdrawal from heroin ("I have the monkey on my back").

munchies
hunger and constant snacking often characteristic of marijuana intoxication.

narc
narcotics law enforcement officer.

needle
hypodermic needle for injecting drugs. *Syn.* spike.

needle freak
refers to individuals who achieve such gratification from the act of injection that they will often inject nonpsychoactive substances merely for the pleasure of the experience.

Needle Park
a formerly infamous traffic island in New York City where heroin addicts and pushers were known to congregate.

nod
a tranquil state occurring shortly after heroin injection, characterized by mild dozing and lolling of the head ("He's on a nod," "He's nodding"). *Syn.* coast.

number two
second narcotics (or other drug-related) conviction, usually carrying a substantially greater penalty than the first conviction.

OD

to take an overdose, usually of a very serious nature ("He OD'd on heroin").

off

abstaining ("She's been off booze since February").

on

(1) to be under the influence of a drug ("He's high on grass");
(2) to use a drug regularly ("He's been on speed for years").

out of sight

(1) of extraordinary quality; wonderful;
(2) a fantastic experience ("That trip was out of sight"). *Syn.* unreal, way out, far out.

outfit

paraphernalia for injecting drugs. *Syn.* fit, kit.

overamped

experiencing agitation and other negative symptoms (possibly as severe as toxic psychosis) resulting from an excessive dose of amphetamines. *Syn.* overcharged.

overcharged

See overamped.

Panama

marijuana grown in Panama. Panama gold and Panama red are considerably more potent than marijuana grown in the U.S. or Canada.

panic

(1) an acute state of fear precipitated by the onset of withdrawal and frantic action to acquire drugs;
(2) an abrupt drying-up of heroin sources, affecting all local addicts.

peace pill

PCP (phencyclidine), probably from PeaCe Pill.

peaches
(from color of tablet) Benzedrine (amphetamine).

peaking
at the period of the most intense effects during an LSD trip.

pearls
amyl nitrite. *Syn.* poppers.

pep pills
amphetamines. *Syn.* peppers, uppers.

pickled
drunk.

pillow
methaqualone.

pinks
(from color of capsule) Seconal (secobarbital). *Syn.* reds, secos, red birds, red devils.

pinned
referring to the contracted pupils (the size of a "pinhead") of someone under the influence of heroin or other narcotic analgesics.

pop
(1) to take a tablet or capsule orally;
(2) to inject subcutaneously. *Syn.* skin pop.

poppers
amyl nitrite, which is administered by crushing (popping) the small vial in which it is contained and immediately inhaling the vapors.

poppy
opium.

pot
marijuana. *Syn.* grass, leaf, etc.

psychedelic
referring to the perception- and consciousness-altering experiences produced by hallucinogenic substances.

powdered
under the influence of cocaine.

purple hearts
(from color and shape) Luminal tablets (phenobarbital).

pusher
seller of drugs at the street level. *Syn.* dealer.

rainbows
Tuinal (a combination of amobarbital and secobarbital), so called because of the bright red and blue capsules. *Syn.* reds and blues.

rap
to discuss, to talk at length.

reds
(from color of capsule) Seconal (secobarbital). *Syn.* pinks, secos, red birds, red devils.

reds and blues
Tuinal. *Syn.* rainbows.

reefer
marijuana cigarette. *Syn.* joint.

right on
exclamation of strong support.

ripped
(1) exhausted after a several-day amphetamine run;
(2) adversely affected by a drug. *Syn.* wrecked, wasted.

ripped off
(1) robbed;
(2) cheated in a drug buy.

rippers
amphetamines. *Syn.* uppers, pep pills.

roach
the butt of a marijuana cigarette, smoked by holding it in a roach "clip" (e.g., bobby pin).

rocket fuel
PCE (cyclohexamine).

roll
to wrap marijuana, tobacco, or similarly prepared substances in cigarette paper ("He rolled a joint").

rope
(from the Indian hemp plant, which contains THC) marijuana. *Syn.* grass, weed, pot, etc.

rummy (rubby)
skid-row alcoholic. "Rubby" is also sometimes applied specifically to those who on occasion resort to isopropyl (rubbing) alcohol.

run
a period of several consecutive days during which an individual injects methamphetamine ("speed") several times a day, usually with little or no food or sleep for the duration.

rush
an intense orgasm-like sensation which rapidly follows intravenous administration of such drugs as heroin, amphetamines, or cocaine. *Syn.* flash, bang.

scag
(outmoded) heroin.

scene
originally a media term used in the 1960s to describe (at least in reference to drugs) patterns of drug use in a locale or among certain groups ("the drug scene"); similar to but not synonymous with another media-originating reference, "the drug subculture."

schoolboy
: codeine; so called because of the mildness of its effects when compared with the more potent narcotic analgesics.

score
: to succeed in making a drug purchase.

scratch
: money.

script writer
: sympathetic physician willing to write a prescription for narcotic analgesics for a user who has faked symptoms.

secos
: Seconal. *Syn.* reds, pinks, etc.

send it home
: to inject narcotic analgesics, cocaine, or amphetamines intravenously.

set-up
: a situation in which undercover police officers entice a person to sell (or in some instances give) them drugs for the purpose of bringing about the person's arrest.

shades
: sunglasses (worn by heroin addicts to conceal their pinpoint pupils).

shakes
: tremors, an early sign of alcoholic withdrawal.

shave
: (1) to adulterate, dilute, or shortweight a drug. *Syn.* cut;
: (2) literally to shave off minute quantities (e.g., of a block of hashish) and thereby shortweight the buyer.

shoot up
: to inject intravenously. *Syn.* mainline.

shooting gallery
a place where heroin addicts congregate to inject.

shortchanged
having been sold drugs which are unusually inferior in quality or purity.

shot in the arm
although the general use of the term is now broader, it originally referred to an injection of narcotics, which is followed by a state of peacefulness, reverie, and well-being.

sickness
the onset of withdrawal ("He's got the sickness").

skin popping
injecting subcutaneously. *Syn.* popping.

sleepers
sedative/hypnotic drugs, such as barbiturates. *Syn.* downers.

smack
heroin. *Syn.* H, horse, junk.

smashed
heavily intoxicated with alcohol or other drugs. *Syn.* bombed, blasted.

smoke
marijuana. *Syn.* grass, pot, weed, leaf, etc.

sniff
(1) to take cocaine, amphetamines, or heroin by inhalation through the nose. *Syn.* snort;
(2) also, to inhale solvents (e.g., as found in glue or model cement) through both the nose and mouth.

snow
cocaine. *Syn.* coke, snowflake(s), stardust.

snow bird
a person dependent on cocaine.

snowflake(s)
cocaine. *Syn.* coke, snow, stardust.

soft drugs
drugs of abuse other than narcotic analgesics; also applied to those drugs perceived to have low toxicity and/or dependence liability.

soaper, soap
Sopor (methaqualone).

soldier's disease
(outmoded) morphine addiction (from the many wounded American Civil War soldiers who were given morphine as an analgesic and became addicted).

spaced
unresponsive to the external environment, usually (although not exclusively) in reaction to altered consciousness produced by hallucinogenic drugs. *Syn.* spaced out.

spacey
alluding to a strangeness or a state of psychic deterioration produced by excessive and/or heavy chronic use of drugs.

speed
injectable methamphetamine. *Syn.* meth.

speedball
heroin plus cocaine (or methamphetamine). *Syn.* bombita.

speed freak
heavy regular user of injectable methamphetamine; usually, a user who exhibits paranoid thinking and is often aggressive and/or unpredictable. *Syn.* speeder.

spike
hypodermic needle for injecting drugs.

split
to leave.

stardust
cocaine. *Syn.* flake, coke, snow.

stash
(1) a place (on one's person, in one's abode, or elsewhere) where drugs are hidden to escape detection in the event of a sudden search by legal authorities;
(2) to hide drugs rapidly when confronted with a search.

step on
to dilute a drug ("This smack's really been stepped on"). *Syn.* cut.

stoned
pleasurably intoxicated. *Syn.* high.

straight
(1) an individual who does not use or who no longer uses drugs ("She's a straight");
(2) a condition of no longer using drugs ("I've been straight for a year").

straighten out
to quit using drugs. *Syn.* get straight.

strung out
(1) in an emaciated and generally poor state of health and appearance due to chronic drug use;
(2) heavily dependent on drugs;
(3) sometimes, to produce an extreme negative psychic effect during a single drug episode ("The acid really strung him out"). *Syn.* bad trip.

supergrass
PCP sprinkled on marijuana and smoked.

sweat it out
to withdraw from narcotic analgesics (from the profuse sweating accompanying withdrawal).

Ts and blues
pentazocine (Talwin) plus tripelennamine (e.g., Pyribenzamine), prepared in solution and injected intravenously.

tabs
tablets or capsules containing LSD.

THC
Δ^9-tetrahydrocannabinol, the active principle in marijuana and hashish.

tie up
to apply a belt or tourniquet to the arm or leg to produce distension of a vein for injection.

tight
drunk or inebriated.

toke
(1) a puff of a marijuana cigarette;
(2) to take a puff of a marijuana cigarette.

toot
cocaine

totaled
exhausted after an acute drug experience. *Syn.* wasted.

tracks, track marks
(1) collapsed veins resulting from chronic injection. *Syn.* lines;
(2) discoloration and scars, resembling a tattoo in appearance, resulting from chronic injection.

tranks
any of the minor tranquillizers. *Syn.* downers.

trip
(1) the experience produced by a hallucinogenic drug;
(2) to take a hallucinogenic drug.

traveler
a user of hallucinogenic drugs.

trippers
LSD.

turn on

(1) to produce a state of pleasurable excitement. The stimulus may be either a drug or other experience ("Rock music really turns me on");

(2) to introduce someone to a drug or to drugs ("He turned him on to grass").

unreal

wonderful, fantastic. *Syn.* out of sight.

up front

(1) as a sample—i.e., a small quantity of a drug is provided to the buyer (usually a middle man or pusher) to indicate its quality;

(2) as proof—i.e., showing the seller the money before the drugs are produced.

up tight

tense, nervous, or frightened because of a subjective experience produced either by a drug or by real events.

uppers

a general term for most stimulant drugs of abuse, such as the amphetamines and related drugs; however, the term is not used for cocaine.

user

one who regularly takes drugs.

vegetable

one who suffers from severe brain or behavioral impairment to the point of being unable to care for oneself.

wasted

(1) exhausted after an acute drug experience, usually in reference to amphetamines ("After two days on speed he was totally wasted"). *Syn.* totaled, wiped out, wrecked;

(2) having had a very bad drug experience. *Syn.* wrecked;

(3) murdered.

way out

wonderful, fantastic. *Syn.* out of sight.

wino
skid-row alcoholic.

wedges
flat LSD tablets.

weed
(1) marijuana. *Syn.* grass, pot, leaf, etc.;
(2) tobacco.

weekend habit
See chippying.

wiped out
exhausted after an acute drug experience. *Syn.* wasted.

wired
(1) chronically dependent on amphetamines;
(2) physically dependent on heroin.

works
paraphernalia for injecting drugs. *Syn.* fit, kit, outfit.

wrecked
(1) exhausted after an acute drug experience;
(2) having had a very bad drug experience. *Syn.* wasted.

yellows, yellow jacks
(from color of capsule) Nembutal (pentobarbital sodium).

yen
agitated sleep occurring during withdrawal from heroin (or other narcotic analgesics).

zonked
extremely high on drugs.

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